FORMULATION AND *IN VITRO* EVALUATION OF FLOATING TABLETS OF LOSARTAN POTASSIUM

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In

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Submitted by

Reg. No - 26103009

Under the guidance of

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND *IN VITRO* EVALUATION OF FLOATING TABLETS OF LOSARTAN POTASSIUM",** submitted by the student bearing **Reg.No. 26103009** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

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Place: Komarapalayam

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DECLARATION

The work presented in this dissertation entitled "**FORMULATION AND *IN VITRO* EVALUATION OF FLOATING TABLETS OF LOSARTAN POTASSIUM"** was carried out by me under the direct supervision of **Mrs**. **S.Bhama, M.Pharm.,** Asst. Professor, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Komarapalayam, in partial fulfillment for the award of the degree of Master of Pharmacy in Pharmaceutics.

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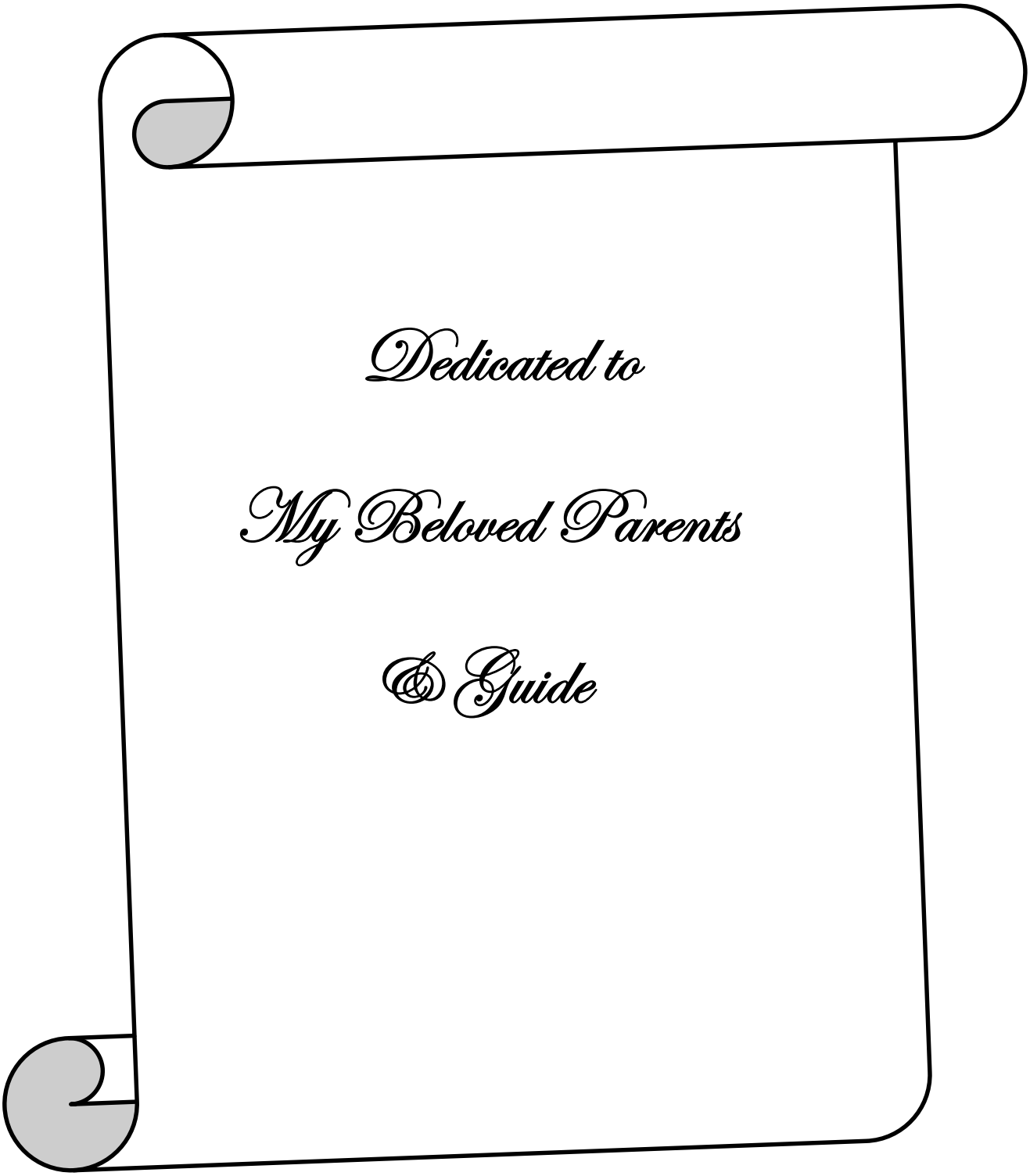
Dedicated to
My Beloved Parents
& Guide

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NAVEEN. MALLAMPATHI.,

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INDEX

ABBREVIATIONS

°C	=	Degree Centigrade
FLT	=	Floating Lag Time
F	=	Formulation
GRDDS	=	Gastroretentive Drug Delivery System
GIT	=	Gastro Intestinal Tract
GRT	=	Gastric Retention Time
HPMC	=	Hydroxypropylmethylcellulose
hr	=	Hour
mg	=	Milligram
min	=	Minute
mL	=	milliliter
n	=	Diffusion coefficient
nm	=	nanometer
rpm	=	Revolution per minute
CRDDS	=	Controlled release drug delivery system
TT	=	Transit time
TFT	=	Total Floating Time
USP	=	United States Pharmacopoeia
UV	=	Ultra violet
mcg	=	microgram
FTIR	=	Fourier Transformed Infrared Spectroscopy

INTRODUCTION

The oral route currently represents the most predominant and preferable route of drug delivery. Unlike majority of parenteral dosage forms, it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body. Oral drug delivery systems have progressed from conventional immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.

CONVENTIONAL DRUG DELIVERY SYSTEM

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms.

The oral dosage form has survived due to

1. Relatively simple and inexpensive to make

2. Convenient for the patient

3. Technology is easy to adapt to changing needs of the drug substance

4. Simplifies the regulatory approval process.

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption (Robinson JR Lee, 1987).

Limitations of the Conventional Drug Delivery System:

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.
4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits (Chien, 1992).

CONTROLLED DRUG DELIVERY SYSTEM (CDDS)

Over the years, as the expense and complications involved in marketing new drug entities have increased with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on the development of modified release dosage forms.

Modified release systems have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects. Oral modified release delivery systems are most commonly used for 1) delayed release (e.g., by using an enteric coating); 2) extended release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release (e.g., for colonic delivery or gastric retention). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics. Delayed release dosage forms are distinguished from the ones mentioned above as they exhibit a pronounced lag time before the drug is released. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration. Extended release DDS include single-unit, such as tablets or capsules, and multiple-unit dosage forms, such as mini tablets, pellets, beads or granules, either as coated (reservoir) or matrix devices.

Controlled Release

Controlled release systems designed to maintain plasma levels in therapeutic range and thus minimize the effects of such problems. Furthermore; controlled release systems reduce the dosing frequency, thereby improving patient compliance and therapeutic efficacy (Christopher et al., 2005).

Sustained Release

Drug products that provide “extended” or “sustained” drug release appeared as a major class of dosage form. Many terms as sustained-release, sustained-action, prolonged- action, controlled-release, extended-release, timed-release, and long-acting have been used to describe product types and features. For the most part, these terms are used to describe orally administered dosage forms, whereas the term rate-controlled delivery is applied to certain types of drug delivery systems in which the rate of drug delivery is controlled by features of the device rather than by physiological or environmental conditions as gastrointestinal pH or drug transit time through the gastro intestinal tract (GIT).

Modified-release

This term has come into general use to describe dosage forms having drug release features based on time, course, and/or location which are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate-release forms.

Extended-release

Extended-release dosage form is one that allows a reduction in dosing frequency to that presented by a conventional dosage form.

Delayed-release

Dosage form is designed to release the drug from the dosage form at a time after administration. The delay may be time- based or based on the influence of environmental conditions, as gastrointestinal pH.

ABSORPTION WINDOWS

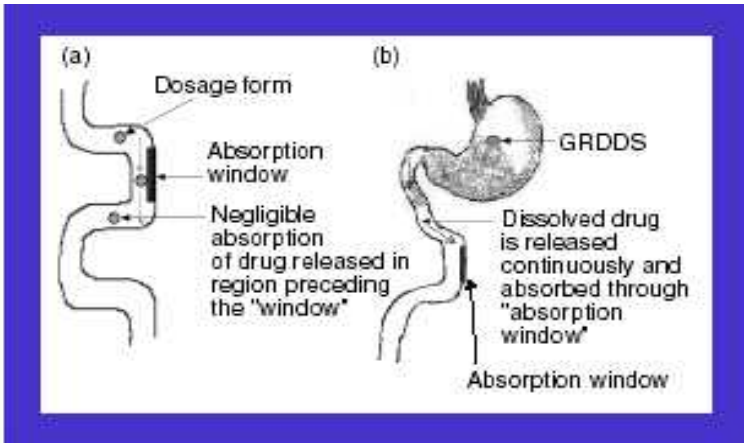
Some drugs display region-specific absorption that can be related to differential drug solubility and stability in different regions of the intestine as a result of changes in environmental pH, degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile. Active transport mechanisms for drugs involving carriers and pump systems have been well described. Compounds such as ACE inhibitors and certain antibiotics exploit peptide transporters. The importance of P-450 metabolism in the intestinal mucosa has now been recognized. The iso form P4503A4 (CYP3A4) is dominant in 'gut wall' metabolism and different levels are found in different regions of the intestine. The absorption of drugs can also be limited by efflux mechanisms, especially if compounds are lipophilic in nature. The secretory transporter P-glycoprotein located on the mucosal surface of epithelial cells is responsible for the low and variable bioavailability of various compounds (e.g.-propranolol, felodipine) some drugs can be substrate for both CYP3A4 and P-glycoprotein (cyclosporine, itraconazole). In theory, it should be possible to inhibit efflux and metabolism processes by the use of inhibitors, but such agents are not usually without their own pharmacological effects. The inhibitory effect of grapefruit juice toward intestinal CYP450 is a well known example.

Today, it is possible to assess regional differences in intestinal drug absorption by conducting non-invasive human drug absorption (HDA) study using a remote controlled delivery capsule. Gamma scintigraphy is used for real-time visualization of capsule location and a radiofrequency signal is used to activate the capsule at the target site. For example, in order to determine the bioavailability and pharmacokinetic profile of faropenem daloxate (a prodrug of broad spectrum antibiotic), this drug was delivered in a particulate form to the proximal small bowel, distal small bowel or ascending colon. The pharmacokinetic profiles for delivery to the two sites in the small intestine were similar and comparable to those for a reference tablet. Significant absorption was also seen after delivery to the colon, but the area under the curve (AUC) and the maximum plasma concentration (C_{max}) values were markedly reduced (Washington et al., 2001)

Concept of absorption window

Drug exhibiting absorption from only a particular portion of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show absorption window which signifies the regions of GI tract from where absorption primarily occurs. Drug released from the CRDDS after the absorption window has been crossed goes waste with no or negligible absorption occurring (Figure 1). This phenomenon drastically decreases the available drug for absorption, after release of drug from CRDDS. The CRDDS possessing the ability of being retained in the stomach are called GRDDS and they can help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability.

Figure1: a) Conventional drug delivery system, (b) GRDDS.



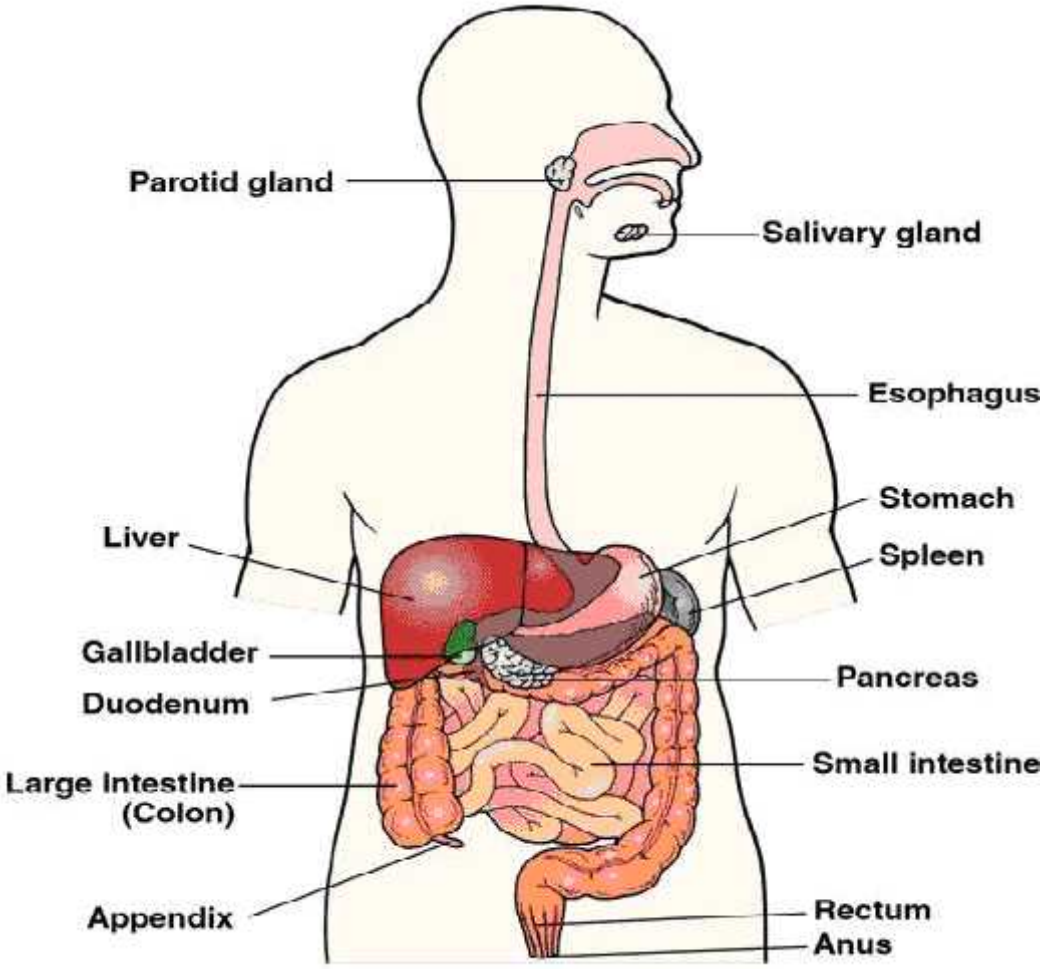
GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Gastro retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of

drug liberation. Basically, gastro retentive system retains in the stomach for a number of hours and continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, Sustained release DDS possessing gastric retention properties may be potentially useful.

ANATOMY AND PHYSIOLOGY OF THE GI TRACT

Figure 2: Structure of the gastrointestinal tract



To comprehend the considerations taken in the design of GRDFs and to evaluate their performance, the relevant anatomy and physiology of the gastrointestinal tract must be fully understood. The basic Structure of the gastrointestinal tract is shown in Fig 2.

The GIT consists of a hollow muscular tube starting from the oral cavity, where food enters, the mouth, continuing through the pharynx, oesophagus, stomach and intestines to the rectum and anus. Anatomical and physiological features of the human GIT are given in Table 1.

Table 1: Anatomical and physiological features of the human GIT

Section	Average length (cm)	Diameter (cm)	Villi present*	Absorption mechanism	pH	Major constituents	Transit time of food (h)
Oral cavity	15–20	10	–	Passive diffusion, convective transport	5.2–6.8	Amylase, maltase, ptyalin, mucins	Short
Esophagus	25	2.5	–		5–6	–	Very short
Stomach	20	15	–	Passive diffusion, convective transport	1.2–3.5	Hydrochloric acid, pepsin, rennin, lipase, intrinsic factor	0.25–3.00
Duodenum	25	5	+	Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis	4.6–6.0	Bile, trypsin, chymotrypsin, amylase, maltase, lipase, nuclease, CYP3A4	1–2
Jejunum	300	5	++	Passive diffusion, convective transport, active transport, facilitated transport	6.3–7.3	Amylase, maltase, lactase, sucrase, CYP3A5	–
Ileum	300	2.5–5.0	++	Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis	7.5	Lipase, nuclease nucleotidase, enterokinase	1–10
Cecum	10–30	7	+	Passive diffusion, convective transport, active transport, pinocytosis	7.5–8.0	–	Short
Colon	150	5	–	Passive diffusion, convective transport	7.9–8.0	–	4–20
Rectum	15–19	2.5	–	Passive diffusion, convective transport, pinocytosis	7.5–8.0	–	Variable

Stomach

The stomach is situated in the left upper part of the abdominal cavity under the diaphragm, between the lower end of the esophagus and the small intestine, and

is the most dilated part of the GIT. Its opening to the duodenum is controlled by the pyloric sphincter. The stomach is divided into three anatomical regions (Figure 4).

i) Fundus

ii) Body and

iii) Pylorus (or antrum)

The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying.(Tortora et al., 1996; Wilson and Waugh, 1989).

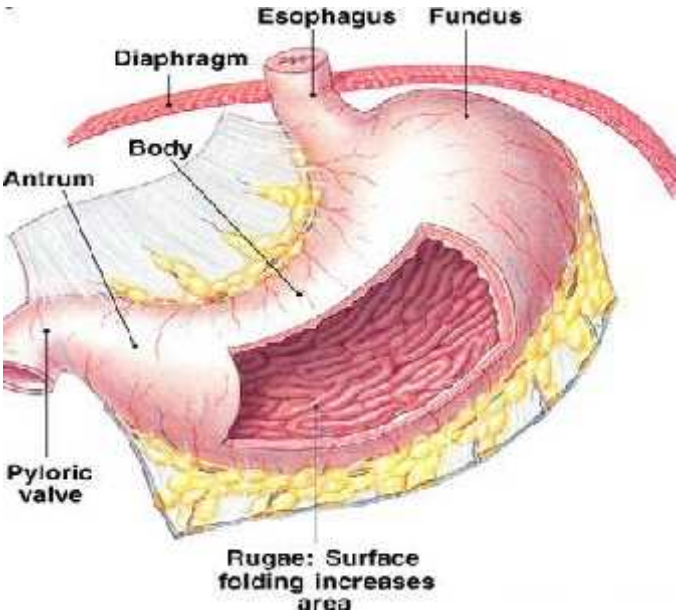


Figure 3: Schematic illustration of the stomach anatomical structure

Small Intestine

The small intestine is composed of the duodenum, jejunum, and ileum. It averages approximately 6m in length. The duodenum is the proximal C-shaped section that curves around the head of the pancreas. The duodenum serves a mixing function as it combines digestive secretions from the pancreas and liver with the contents expelled from the stomach. The start of the jejunum is marked by a sharp bend, the duodeno jejunal flexure. It is in the jejunum where the majority of digestion and absorption occurs. The final portion, the ileum, is the longest segment

and empties into the caecum at the ileocaecal junction. The small intestine has a large surface area, which is comparable to the area of a basketball court, 463 m^2. This is the main reason it is the primary absorption site of water, ions, vitamins and nutrients such as amino acids, fats and sugars. In addition, the digestion of fats, peptides and sugars occurs in this segment of the gastrointestinal tract. The pH of the small intestine is 6–7. The transit time in the small intestine of 361 h, is relatively constant and is unaffected by food.

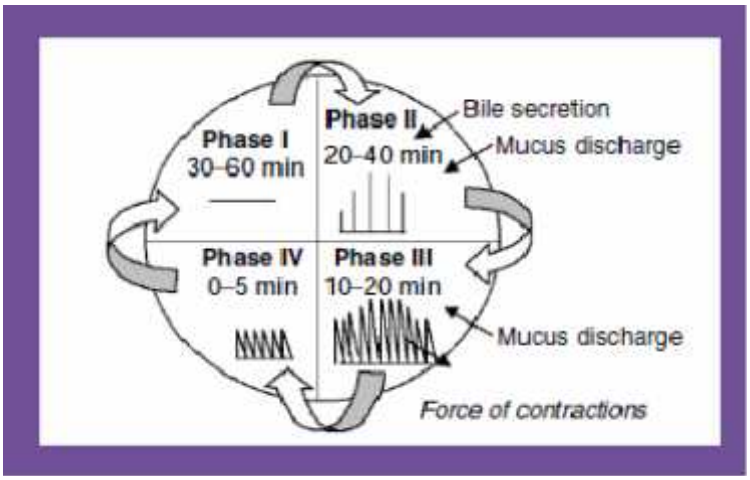
Large Intestine

The colon has some absorption properties of water and ions. Certain drugs and especially peptide molecules are also absorbed. This is despite the lack of villi, which leads to small surface area.

GASTRIC EMPTYING

The time a dosage form takes to traverse the stomach is usually termed the 'gastric emptying rate'. Gastric emptying of Pharmaceuticals is highly variable and is dependent on dosage form. The process of gastric emptying occurs during fasting as well as fed states. However, the pattern of motility is distinct in the 2 states. In the fasting state, it is characterized by an inter digestive series of electrical events that cycle both through stomach and small intestine every 2 to 3 hours. This activity is called the inter digestive myo electric cycle or migrating myo electric cycle (MMC), which is further divided into following 4 consecutive phases (Figure 4) as described by Wilson and Washington.

Figure 4: motility patterns of the GIT in the fasted state



- **Phase I (Basal phase)** lasts from 40 to 60 minutes with rare contractions.
- **Phase II (Pre burst phase)** lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- **Phase III (Burst phase)** lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- **Phase IV** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

The motor activity in the fed state is induced 5-10 min after ingestion of a meal and persists as long as food remains in the stomach. It consists of regular and frequent contractions. These contractions are not as severe as those in the third phase of the fasted motility pattern. The G.I. Transit times of dosage forms in the various segments of the G.I. tract are listed in Table 2.

Table 2: Transit times of various dosage forms across the segments of the GIT.

Dosage form	Transit time (h)		
	Stomach	Small intestine	Total
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.5	4.4

Gastric pH

The gastric pH is influenced by many factors like diet, disease, presence of gases or fatty acids, and other fermentation products (Rubinstein, 1990), age (Varis et al., 1979), pathological conditions drugs, as well as intra- and inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs. Radiotelemetry, a noninvasive device, has successfully been used to measure the gastrointestinal pH in humans. It has been reported that the mean value of gastric pH in fasted healthy males is 1.7 ± 0.3 (Chung et al., 1986; Dressman et al., 1990; Russell et al., 1993), while that of females was reported to be slightly lower. On the other hand, in the fed state, the mean gastric pH in healthy males has been reported to be between 4.3 – 5.4 (Dressman *et al.*, 1990), and the pH returned to basal level in about 2 to 4 hours.

About 20% of the elderly people exhibit either diminished (hypochlorohydria) or no gastric acid secretion (achlorohydria) leading to basal pH value over 5.0 (Varis *et al.*, 1979). Pathological conditions such as pernicious anemia and AIDS may significantly reduce gastric acid secretion leading to elevated gastric pH. In addition, drugs like H2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion.

Hence, the gastric pH is an important consideration when selecting a drug substance, excipients, and drug carrier for designing intra gastric delivery systems.

FACTORS AFFECTING GASTRIC RETENTION OF DOSAGE FORMS

- **Density:** Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density of a dosage form which affects the gastric emptying rate. A buoyant dosage form should have a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.
- **Size:** Dosage form units having a diameter of more than 7.5 mm are reported to have an increased gastric residence time compared with those having a diameter of 9.9 mm. Gastric retention time of a dosage form in the fed state can also be influenced by its size. Small tablets are emptied from the stomach during the digestive phase while large .size units are expelled during the house keeping waves.
- **Shape of dosage form:** Different shapes (ring, tetrahedron, cloverleaf, disk, string and pellet) displays different gastric retention times, due to their size and geometry of the systems,.The tetrahedron resided in the stomach for longer periods than other devices of a similar size; likewise extended gastric retention was observed with rigid rings .Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) have a better gastric residence time as compared with other shapes and had been reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as meals were given at the

time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

- **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release. (Timmermans *et al,* 1994)
- **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats. (Marvola *et al.,* 1989).
- **Frequency of feed:** The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.
- **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anti cholinergics like atropine and Propantheline, opiates like codeine and pro kinetic agents like Metoclopramide and Cisapride (Mojave Ian et al., 1988).
- **Biological factors:** Diabetes and Crohn's disease can affect the gastric retention time.

DRUG CANDIDATES FOR GASTRIC RETENTION

Gastro retentive DDSs exhibiting controlled drug release are significantly important for drugs which are:

- Acting locally in the stomach (e.g. antibiotics against Helicobacter Pylori, antacids and Misoprostol) (Burton *et al.,* 1995; Fabregas *et al.,* 1994; Oth et al., 1992; Whitehead *et al*., 2000; Whitehead *et al.,* 1996).
- Absorbed incompletely due to a relatively narrow window of absorption in the GIT, such as Cyclosporin, Ciprofloxacin, Furosemide, L-DOPA, *P*-aminobenzoic acid and Riboflavin. (Hoffman *et al.,* 2004; Ichikawa *et al.,* 1991a; Klausner *et al*., 2003d; Levy and Jusko, 1966; Rouge *et al*., 1996).
- Unstable in the intestinal or colonic environment such as Captopril
- Exhibit low solubility at high pH values such as Verapamil HCl, Diazepam and Chlordiazepoxide (Elkheshen *et al.,* 2004; Soppimath *et al.,* 2001).

In general the group of drugs, that benefits from an oral application using a gastro retentive DDS, includes analgesics, antibiotics, tranquilizers, diuretics, antidepressants, vitamins, hormones, antacids and anti parkinsonian drugs (Hoichman *et al.,* 2004).

Gastro retentive DDS, on the other hand, are not suitable for drugs that may cause gastric lesions, e.g., non-steroidal anti-inflammatory agents and drug substances that are unstable in the strong acidic environment of the stomach. In addition, gastro retentive systems do not offer significant advantages over conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract (Talukder and Fassihi, 2004). It is recognized, however, that there are many physiological constraints which may limit development of such delivery systems.

APPROACHES TO GASTRIC RETENTION

Various approaches have been pursued to increase the retention of oral dosage forms in the stomach. The most common approaches used to increase the gastric residence time of pharmaceutical dosage forms include

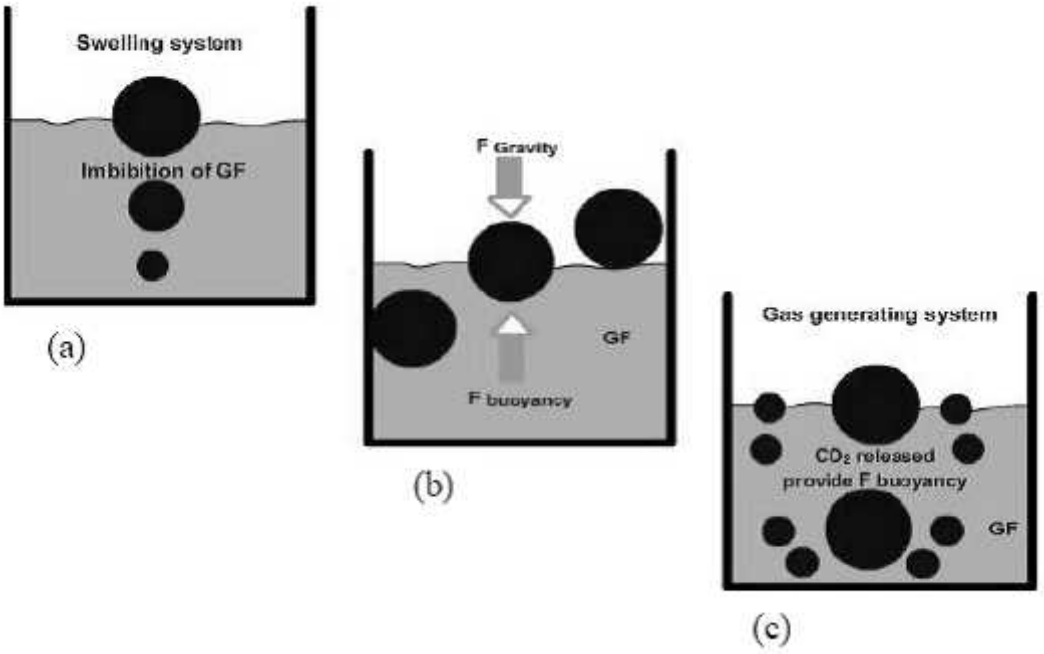
- Floating systems
- Swelling and expanding systems
- Bio adhesive systems
- Unfolding and modified- shape systems
- High density systems
- Others.

FLOATING SYSTEMS

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (mechanism given in Figure 5), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

Most floating systems reported in the literature are single unit systems, such as HBS and floating tablets. The systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered due to their all or nothing empting process (Kawashima et al., 1991). On the other hand, multiple unit dosage forms, such as hollow microsphere (micro balloons), granules, powder, and pellets, are more suitable since they are claimed to reduce the inter- and intra-subject variability in absorption and reduce the probability of dose dumping (Rouge et al., 1997).

Figure 5: Mechanism of floating systems



Types of floating drug delivery systems (FDDS)

Floating properties based on the mechanism of buoyancy are divided into:

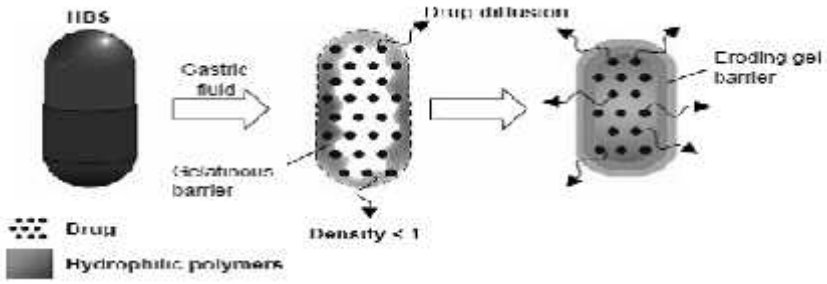
1. **Non effervescent systems** with inherent low density or low density due to swelling; and
2. **Effervescent systems** with low density due to gas generation and entrapment.

Non- Effervescent Systems

A) Hydro dynamically Balanced Systems

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface (Dubernet et al., 2004). Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Reddy et al., 2002) (Figure 6).

Figure 6: Hydro dynamically balanced system



Hydro dynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with Chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/mL and is ~0.1 mg/mL at neutral pH).

B) ALGINATE BEADS

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours. (Katayama *et al.*, 1999).

C) HOLLOW MICROSPHERES / MICROBALLONS:

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h *in vitro* (Kawashima, 1992).

Floating micro particles based on low-density foam powder has been proposed and its performance investigated *in vitro* (Streubel *et al.,* 2002). The floating micro particles were prepared with an oil-in-water solvent extraction/evaporation method and were composed of polypropylene foam powder; verapamil HCl as the model drug; and a controlled release polymer, Eudragit® RS, EC or polymethyl methacrylate (PMMA). The micro particles were irregular in shape and highly porous. Good *in vitro* floating behaviour was observed. The increase in drug release was proportional to the drug loading and inversely proportional to the amount of polymer and the release profile varied with varying the polymer type.

Effervescent Systems (Gas-generating systems):

This approach provides floating drug delivery systems based on the formation of CO_2 gas. It utilizes effervescent components such as sodium bicarbonate (NaHCO3) or sodium carbonate, and additionally citric or tartaric acid (Rubinstein and Friend, 1994). Alternatively matrices containing chambers of liquids that turns into gas at body temperature could be used. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on gastric contents.

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), and effervescent components

(e.g., sodium bicarbonate, citric acid or tartaric acid).The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxyl propyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc. (Rubinstein A et al., 1994; Stockwell AF et al., 1986).

Ichikawa *et al* developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability, independent of pH and viscosity and the drug released in a sustained manner

Figure7. (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating ;(C) Dissolution of drug.

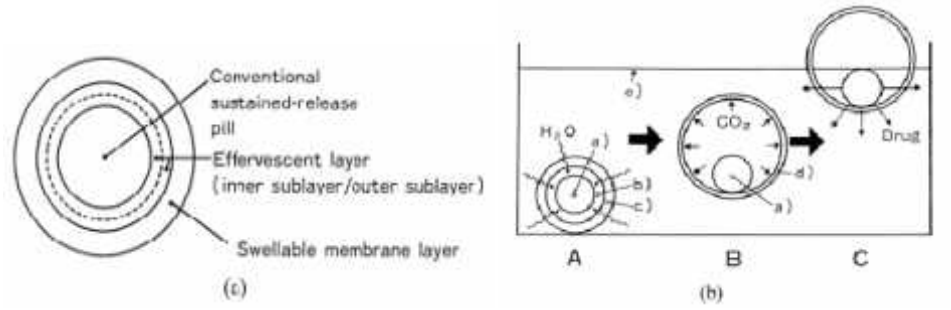


Table 3: List of drugs prepared as FDDS

S.No.	DOSAGE FORM	DRUGS
1.	Microspheres	Metformin hydrochloride, ketoprofen, Aspirin, Verapamil, Grisiofulvin, *P*-nitroanilline, Ibuprofen,
2.	Granules	Diclofenac sodium, Indomethacin, Prednisolone
3.	Films	Cinnarizine
4.	Powders	Several basic drugs
5.	Capsules	Chlordiazepoxide HCl, Diazepam, Frusemide, L-Dopa and Benserazide, Misoprostol, Propranolol
6.	Tablets/Pills	Phenytoin hydrochloride,5 fluoro uracil, Furosemide, Ciprofloaxacin, pentoxyfillin, Atenolol,

Table 4: List of drugs which are marketed as FDDS

Brand name	Drug	Clinical Importance	Dosage form
Madopar®	Levodopa Benserazide	Parkinsonism	Capsule

Cytotec®	Misoprostal	Gastric ulcer	Capsule
Valrelease®	Diazepam	Sedative –hypnotic	Capsule
Conviron	Ferrous sulphate	Pernicious anemia	Capsule
Liquid Gavison®	Al. hydroxide, Mg. carbonate	Heart burn	Liquid alginate preparation
Topalkan®	Al-Mg antacid	Antacid	Liquid alginate preparation
Cifran OD®	Ciprofloxacin	Urinary tract infection	Tablet
Oflin OD®	Ofloxacin	Genital Urinary, respiratory, Gastro-intestinal infection	Tablet
Prolopa®	Propranolol	Hypertension	Tablet
Amalgate Flotacoat®	Amalgate	Antacid	Tablet
Halo™	Propranolol	Hypertension	Tablet

Raft-Forming Systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles (Figure 8) on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment.

Figure 8: Schematic illustration of the barrier formed by a raft-forming system

Low-density systems

SWELLING AND EXPANDING SYSTEMS

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter (Caldwell et al., 1988). However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release.

The expansion of this type of DDS is generally due to the presence of specific hydrogel formers, which after swallowing; drastically increase in size upon contact with aqueous media. This increase in size prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as the ***"plug type systems"*** since they exhibit a tendency to remain lodged at the pyloric sphincter. Caldwell *et al.,* 1988 proposed different geometric forms (tetrahedron, ring or planar membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule.

BIOADHESIVE SYSTEMS

This approach is used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner (Itoh *et al.,* 1986). A bioadhesive can be defined as a substance with the ability to interact with biological materials and is capable of being retained on the biological

substrate for a period of time. Bioadhesion always occurs in the presence of water (Andrews *et al.,* 2009; Park and Robinson, 1985).

It involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GIT. These are usually macromolecular, hydrophilic gelling substances with numerous hydrogen-bond forming groups, such as carboxyl, hydroxyl, amide and sulfate groups (e.g., crosslinked polyacrylic acids, sodium carboxymethyl cellulose (CMC), sodium alginate and carrageenan). A broad spectrum of polymers was studied for their bioadhesive properties. It was concluded that anionic polymers have better binding capacity than neutral or cationic polymers (Lehr, 1994; Pardeep K. Gupta *et al.,* 1990). The proposed mechanism of bioadhesion is the formation of hydrogen – and electrostatic bonding at the mucus-polymer boundary (Pardeep K. Gupta et al., 1990), although it is not yet clear. Rapid hydration in contact with the muco-epithelial surface appears to favour adhesion.

UNFOLDING AND MODIFIED- SHAPE SYSTEMS

These are non disintegrating geometric shapes moulded from silastic elastomer or extruded from polyethylene blends, which extend the gastric residence time depending on size, shape and flexural modulus of the drug delivery device (Caldwell, 1988a, 1988c; Cargill *et al.*, 1988).

Devices with different geometrical shapes such as continuous solid stick, tetrahedron, ring, cloverleaf, planer disk, string and pellet/sphere were investigated (Caldwell, 1988c, 1988a, 1988b). These systems consist of at least one erodible polymer (e.g., Eudragit® E, hydroxy propyl cellulose (HPC)), one non erodible polymer (e.g., polyamides, poly olefins, polyurethanes), and a drug dispersed within the polymer matrix. Cloverleaf, disk, string and pellet shapes were moulded from silastic elastomer, while tetrahedron and rigid-ring shapes were fabricated from blends of low-density polyethylene and ethylene: vinyl acetate copolymer. The devices are compressible to a size suitable for swallowing within a capsule, and are self-expandable to a size, which prevents their passage through the pylorus. Furthermore, they are sufficiently resistant to forces of the stomach to prevent rapid passage through the pylorus for a pre-determined period of time, and erode in the presence of gastric juices.

In vivo studies in beagle dogs have been performed to study the systems physical characteristics, such as size, shape and flexibility on the gastric emptying (Cargill et al., 1988), after they were folded and placed in a gelatin capsule. The tetrahedron-shaped devices remained in the stomach for longer periods of time than the other shapes, while strings and pellets were eliminated fairly rapidly.

Other shapes, which can be packed into gelatin capsules and increase in size following unfolding, include Y-shaped systems and sheet-like shaped devices.

HIGH DENSITY SYSTEMS

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and IRO powder, etc. These materials increase density by up to 1.5–2.4g/cm-3.

MAGNETIC SYSTEMS

This system is based on a simple idea: The dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito et al., 1990 used this technique in the rabbits with bioadhesive granules containing ultra fine Ferrite (γ-Fe_2O_3). This guided them to the esophagus with an external magnet (~1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 hrs.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage forms at the site of absorption and thus enhances the Bioavailability. These are summarized as follows.

I. Sustained Drug Delivery

Sustained drug absorption from oral controlled release dosage form is often limited due to short gastric retention time. However, GFDDS remain in the stomach for several hours to their increased GRT. It has been suggested that due to their low density than their gastric contents and relatively large size they do not pass through the pylorus that has an opening of approximately 0.9-1.9cm. It has been observed that major portion of drug relerases in the colon rather than the stomach in case of modified release capsule. However, prolongation in the GRT may sustain the drug .release behaviour.

II. Site Specific Drug Delivery

Drugs having absorption sites in the upper small intestine like furosemide and riboflavin are typically formulated in the floating dosage forms. It has been reported that absorption of furosemide takes place mainly through stomach followed by duodenum. This characteristics of furosemide prompted scientists to develop a monolithic floating system, which could prolong the GRT and thereby increase the Bioavailability. GFDDS serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted.

III. Absorption or Bioavailability Enhancement

Drugs that have poor Bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the Bioavailability of floating dosage forms could be achieved.

IV. Fewer Doses: Creating once daily formulations for improved patient compliance.

V. Improved plasma levels: Both extends plasma concentration levels and provides a more linear release profile.

VI. Better Bioavailability: Delivers the drug in the upper G.I. tract for optimal absorption

VII. Less Irritation: The polymer matrix acts as a buffer between harsh drug crystals and the stomach lining.

VIII. Fewer side effects: Keeps drugs out of the lower GI tract which can be harmful to intestinal flora. Lower peak concentrations can also reduce adverse pharmacological effects.

IX. Low risk inactive ingredients: Tablets are composed of well .understood polymers from the FDA.s inactive ingredients list. This keeps the regulatory risks and hurdles of the formulation to an absolute minimum.

X. Manufacturing ease: Tablets are made in standard high-speed tableting equipment. No special tooling or engineering is required. The enables high quality, consistent, rapid scale-up and technology transfer to our development and marketing partners.

XI. Low cost: The ingredients used in these systems are commodity items, produced in extremely large quantity and at very low cost.

Disadvantages of Gastroretentive Drug Delivery System

1. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted.
2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system (Hou et al., 2003).
4. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted exactly or accurately.

5. Gastric emptying of floating forms in supine subjects may occur at random and become highly dependent on the diameter. Therefore, patients should not be dosed with floating forms just before going to bed.
6. High variability in gastric emptying time due to variations in emptying process.
7. Unpredictable bioavailability.

LIMITATIONS

1. The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery i.e. upto 400ml of gastric fluids should be present for optimum buoyancy. However, this limitation can be overcome by coating the dosage form with bioadhesive polymers, which easily adhere to the mucosal lining of the stomach and retain. The dosage form can be administered with a glass full of water (200-250 ml) to provide the initial fluid for buoyancy.
2. Floating system is not feasible for those drugs that have solubility problems in gastric fluids.
3. Drugs that are not stable at gastric pH are not suitable candidates to be formulated as GRDDS.
4. Drugs that irritate the mucosa are not suitable candidates and should be avoided to be formulated as GRDDS.
5. The drugs, which have multiple absorption sites in the gastrointestinal tract and are absorbed throughout gastrointestinal tract, which under significant first pass metabolism, are not desirable candidates.
6. Some drugs present in the floating system cause irritation to gastric mucosa.
7. Single unit floating capsules or tablets are associated with an all or none concept, but this can be overcome by formulating multiple unit systems like floating microspheres or microballoons.

EVALUATION OF GRDDS

Any drug product must be evaluated to ensure its performance characteristics and to control batch-to-batch quality. In addition to routine tests for general appearance, hardness, friability, drug content, weight variation, uniformity of content, disintegration time, and drug release, the gastro retentive performance of GRDDS must be evaluated.

FLOATING SYSTEMS

Floating/buoyancy time: The test for buoyancy is usually determined in 900 mL of simulated gastric (HCl/NaCl with 0.02% Tween 80, pH 1.2) or intestinal fluids KH2PO4/NaOH buffer with 0.02% Tween 80, pH 7.4) maintained at 37^0C using the USP dissolution apparatus. These fluids simulate the surface tension of human gastric juice (35–50 mN/m^2). The amount of time the dosage form floats is termed the floating time. In the case of floating microparticles, the number of floating particles and the time during which they remain buoyant on the test solution can be determined. The floating process depends on the balance between the weight and volume of the dosage form. An increase in the buoyancy force caused by the increased volume causes a resultant weight increase and leads to dosage-form flotation.

Specific gravity: The specific gravity of floating systems can be determined by the displacement method, using benzene as a displacing medium.

BIO/MUCOADHESION SYSTEMS

Bioadhesive strength: The bioadhesive strength of a polymer can be determined by measuring the force required to separate the polymer specimen sandwiched between the layers of either an artificial (e.g., cellophane) or biological (e.g., rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer.

SWELLING SYSTEMS

Weight gain and water uptake (WU): The swelling behaviour of a dosage unit can be measured by studying its weight gain or WU. The study is done by immersing the

dosage form in simulated gastric fluid at 37^0C and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in terms of percent weight gain, as given by the following equation

$$WU = (W_t - W_0) \times 100/W_0$$

In which,

W_t and W_0 are the weights of the dosage form at time *t* and initially, respectively

Furthermore, the GRDDS should be evaluated for gastro retention and drug-release behaviour.

METHODS TO ASSESS *IN VIVO* GASTRORETENTION OF GRDDS

Unlike other formulations, the kinetics of transit of the GRDF along the GI tract, and especially in determining its GRT are very important. It requires, in most cases, an imaging technique that can locate the GRDF in vivo. The following methods have been utilized so far to assess gastroretentivity.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a noninvasive technique that is not associated with radioactivity and allows observation of the total anatomical structure in relatively high resolution. The visualization of the GI tract by MRI has to be further improved by the administration of contrast media. For solid DFs, the incorporation of a super paramagnetic compound such as ferrous oxide enables their visualization by MRI. The technique is safe and allows obtaining many pictures from the same subject.

Radiology (X-ray)

In this technique, a radio-opaque material has to be incorporated in the DF, and its location is tracked by X-ray pictures. The technique is used to evaluate gastroretentivity of GRDFs and the disintegration rate of DFs *in vivo*, and also to determine the esophageal transit. Although it is considered cheap and a simple method to use, its major disadvantage is the safety issue owing to repeated exposure to X-ray that increase the risk for the volunteers.

γ- Scintigraphy

Gamma scintigraphy relies on the administration of a DF containing a small amount of radioisotope, e.g., 152Sm, which is a gamma ray emitter with a relatively short half-life. The isotope has to be incorporated into the GRDF in advance. Then, a short time prior to the study, the formulation has to be irradiated in a neutron source that causes it to emit *g* rays. The emitted ray can be imaged using a ‘‘gamma camera’’-a form of a scintillation counter, combined with a computer to process the image, and thereby the DF can be tracked in the GI tract. This technique is elegant and provides proper assessment of gastroretentivity in humans.

Gastroscopy

Gastroscopy is commonly used for the diagnosis and monitoring of the GI tract. This technique utilizes a fiber optic or video system and can be easily applied for monitoring and locating GRDFs in the stomach. However, it is too inconvenient to conduct the procedure frequently in the same experiment for one subject. In human, the procedure can be applied with or without slight anesthesia while it requires complete anesthesia in dogs.

HYPERTENSION

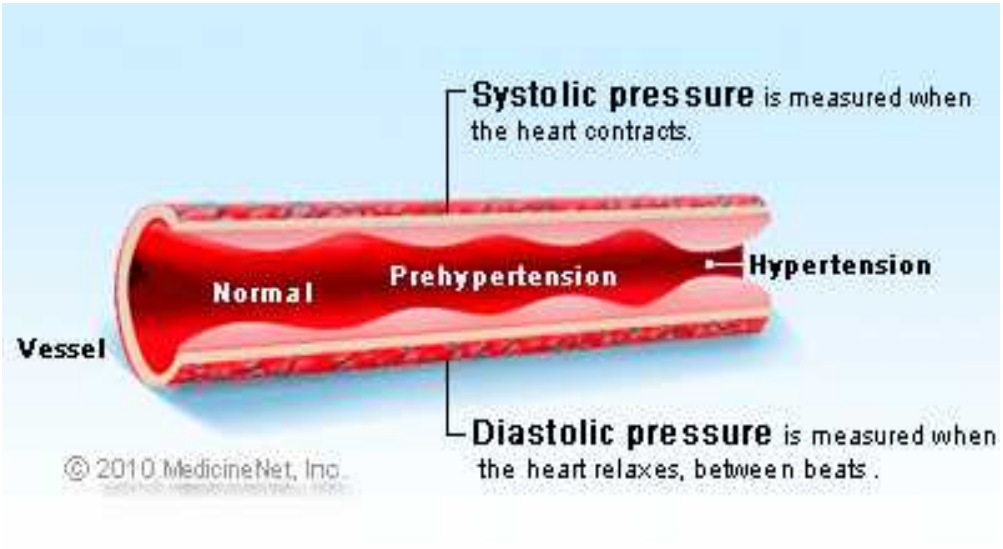


Figure 9: hypertension

- Normal blood pressure less than 120/80
- Pre-hypertension 120-139/ 80-89
- High blood pressure (stage 1) 140-159/90-99
- High blood pressure (stage 2) higher than 160/100

Antihypertensive Drugs

Most antihypertensive drugs can effectively reduce mildly elevated blood pressure, but their use is associated with many side effects. Thus the decision whether to use a drug to control borderline or mild hypertension is made on the basis of the benefit: risk ratio.

Antihypertensive Drugs Classification

Drugs influence arterial blood pressure at four effector sites- arterioles (resistance vessels); veins (capacitance vessels); heart; and the kidneys—by several different

mechanisms. They can be classified according to their site or mode of action as follows:

Diuretics

(i) Thiazides and related agents (hydrochlorothiazide, chlorthalidone etc.)

(ii) Loop diuretics (frusemide, bumetanide, ethacrynic acid)

(iii) Potassium-sparing diuretics (spironolactone, triamterene, amiloride)

II **Sympatholytic Drugs**

(i) Centrally acting agents (methyldopa, clonidine).

(ii) Ganglion blocking agents (trimethaphan).

(iii) Adrenergic neuron blocking agents (guanethidine, guanadrel, reserpine).

(iv) Beta-adrenoceptor blockers (metoprolol, atenolol etc.)

(v) Alpha-adrenoceptor blockers (prazosin, terazosin, doxazosin, phenoxybenzamine).

(vi) Alpha+beta blockers (labetalol, carvediol).

III. **Vasodilators**

(i) Arterial (hydralazine, minoxidil, diazoxide)

(ii) Arterial and venous (nitroprusside)

IV. **Calcium Channel Blockers**

Verapamil, nifedipine, nicardipine, nitrendipine.

V.Angiotensin Converting Enzyme Inhibitors

Captopril, enalparil.

VI. **Angiotensin II Receptor Blockers**

Losartan, valsartan

Antihypertensive Angiotensin II Receptor Blockers

The older agent, saralasin is an Angiotensin II analogue, and a competitive inhibitor of Angiotensin II at both its receptors (AT1 and AT2 sites). It blocks the pressor and aldosterone releasing effects of Angiotensin II, and lowers BP in high rennin states like renal artery stenosis and ischemia.

Losartan

Losartan is a recently introduced blocker of the AT1 receptor. It has no effect on bradykinin metabolism, and therefore a moré selective blocker of Angiotensin effects than the ACE inhibitors.

Panagiotis *et al.*, (2011) investigated the use of nimodipine–polyethylene glycol solid dispersions for the development of effervescent controlled release floating tablet formulations. Nimodipine were optimized in relation to drug release (% release at 60 min, and time at which the 90% of the drug was dissolved) and floating properties (tablet's floating strength and duration), employing a 25-run D-optimal mixture design combined with artificial neural networks (ANNs) and genetic programming (GP).

Ray *et al.*, (2010) was developed an optimal gastro retentive drug delivery system (GRDDS) for administering Losartan. Additionally, the influence of optimized GRDDS on the bioavailability of Losartan and the formation extent of active metabolite E3174 by CYP2C9 polymorphism was investigated. Swellable and floatable GRDDS tablets combining hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC), and sodium bicarbonate were prepared at various compression pressures for evaluating swelling characteristics and floating capacity.

Londhe *et al.*, (2010) was developed Verapamil hydrochloride bi-layer floating tablets have two layers one immediate release layer and second floating sustained release layer. Verapamil hydrochloride bi-layer floating tablet releases drug in two phases i.e. immediate and sustained drug release. Direct compression method was used to formulate bi-layer floating tablets. All bi-layer formulation float more than 12 h and sustained drug release above 12 h.

Libo *et al.*, (2009) designed to assess the safety, tolerability and pharmacokinetics of phenoprolamine hydrochloride floating sustained tablets (PHFST) in healthy Chinese subjects. Safety and tolerability were appraised by monitoring adverse events and laboratory parameters. Pharmacokinetics was assessed by determining the plasma concentrations of phenoprolamine hydrochloride with a validated HPLC method.

Mina *et al.*, (2009) was developed a gastro retentive controlled release drug delivery system with swelling, floating, and adhesive properties. Ten tablet formulations were designed using hydroxypropylmethylcellulose (HPMC K15M) and/or sodium alginate (Na alginate) as release-retarding polymer(s) and sodium bicarbonate (NaHCO3) or calcium carbonate (CaCO3) as a gas former. Swelling ability, floating behavior, adhesion period and drug release studies were conducted in 0.1 N HCl (pH 1.2) at 37 ± 0.5 C. The tablets showed acceptable physicochemical properties.

Anand *et al.*,(2009) novel gastro retentive controlled release drug delivery system of verapamil HCL was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. In vitro drug release studies were performed, and drug release kinetics was evaluated using the linear regression method.

Chen *et al.*, (2010) Investigated the effect on compression pressure using appropriate ratio of Hydroxy ethyl cellulose to sodium carboxymethyl cellulose (NaCMC), and sodium bicarbonate on losoratan tablets. He concluded that compression at low pressure resulted in tablet floating over SGF for more than 16 h and swelling to 2 cm in diameter within 3 h.

Anil *et al.*, (2009) prepared floating delivery system of Ciprofloxacin Hydrochloride using combination of polymers like Hydroxypropyl methylcellulose (HPMC), crospovidone, sodium starch glycolate and croscarmelose sodium. He concluded that combination of HPMC K100M, crospovidone, sodium bicarbonate showed good swelling, drug release, and floating characters.

Srisagul *et al.*, (2008) Floating multi-layer coated tablets were designed based on gas formation. The system consists of a drug-containing core tablet coated with a

protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. The obtained tablets enabled to float due to the CO_2 gas formation and the gas entrapment by polymeric membrane. The increased amount of a gas forming agent did not affect time to float but increased the drug release from the floating tablets while increasing coating level of gas-entrapped membrane increased time to float and slightly retarded drug release.

Strubing *et al.*, (2008a) investigated the mechanism of floating and drug release behavior of poly(vinyl acetate)-based floating tablets with membrane controlled drug delivery. MRI studies of selected samples were performed and the results suggested that the drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics.

Patel *et al.*, (2007a) used hydroxypropyl methylcellulose, ethyl cellulose, and sodium bicarbonate to prepare floating tablets and optimization was done using a simplex lattice design. All the tablet formulations remained buoyant for more than 12 h and the release profile of the optimized batch fitted best to the zero order model.

Bomma *et al.*, (2009) developed floating matrix tablets of norfloxacin to prolong gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by the wet granulation technique, using polymers such as hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M) and xanthan gum. Non-Fickian diffusion was confirmed as the drug release mechanism from these tablets, indicating that water diffusion and polymer rearrangement played an essential role in drug release.

Lingam *et al.*, (2008) Developed floating multiple mini tablets of Ranitidine HCL based on gas formation technique. The system consists of loading dose as uncoated core units, and prolonged-release core units are prepared by direct compression process; the latter were coated with three successive layers, one of which is seal coat,

an effervescent (sodium bicarbonate) layer, and an outer polymeric layer of polymethacrylates. He concluded rapid floating and controlled release properties were achieved.

Patole *et al.*, (2006) developed floating pulsatile drug delivery system for sequential release of aceclofenac. A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in distal small intestine after a defined time period of no drug release. The spherical matrix pellets of drug and pH-dependent polymer Eudragit S-100 were prepared by extrusion spheronization process followed by layering with effervescent component (sodium bicarbonate) using HPMC K100M. The ratios of sodium bicarbonate to HPMC K100M were 2:8, 5:5 and 8:2 w/w. The pellets are layered with an effervescent agent to achieve a weight gain of 10, 30, 50 and 70%. Developed formulations showed instantaneous floating with sequential release of aceclofenac having initial lag time during floating in acidic medium followed by rapid release in basic medium.

Whitehead *et al.*, (2000) prepared floating alginate beads from alginate solution contain either dissolved or suspended amoxicillin. Drug release studies showed that beads prepared with the drug in solution provides some sustained release characteristics and it could be improved by the addition of amylase. The beads retained their buoyancy when amylase and amoxicillin were incorporated, exhibiting resultant weight values greater than zero after 20h.

AIM AND OBJECTIVE

AIM

The main aim of the study was to formulate Losartan potassium floating tablets and evaluation of the tablet. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e. gastro retentive dosage forms (GRDFs), will provide us with new and important therapeutic options.

OBJECTIVE

Losartan is antagonist of angiotensin type I receptor leading to antihypertensive activity by blocking the effects of angiotensin II which include vasoconstriction and aldosterone-secretion effects. Losartan is slightly soluble in water which is having half life of 2 hrs and the bioavailability of Losartan is 33% . To increase the bioavailability of Losartan it would be beneficial to develop a floating drug delivery system that delays the first pass metabolism prolongs gastric residence time and releases drug in GI tract, where absorption of Losartan is more confined. The objective of this research work is to obtain better delivery of Losartan to the stomach and the proximal parts of the small intestine by increasing the mean residence time (MRT) in the stomach. For this, floating tablets are prepared to prolong the gastric emptying that provides maximum drug at the site of absorption.

- The present work is aimed at preparing gastric retentive floating matrix tablet formulations of Losartan using various polymers. The composition of these formulations will be selected by using trial and error methods.
- To study the effect of various factors like drug polymer ratio and polymer grade on the parameters like duration of buoyancy and release rate.

PLAN OF WORK

The present study was proposed to carry out in the following phases for formulation and evaluation of sustained release floating matrix tablets of Losartan potassium.

Phase-I:

1. Pre-formulation study of pure drug
2. Compatibility study

   Fourier transform infrared spectroscopy (FT-IR)
3. Preparation of standard curve of Losartan potassium

   In pH 1.2, 0.1N HCL buffer

Phase-II:

Formulation and evaluation of sustained release floating matrix tablets of Losartan potassium

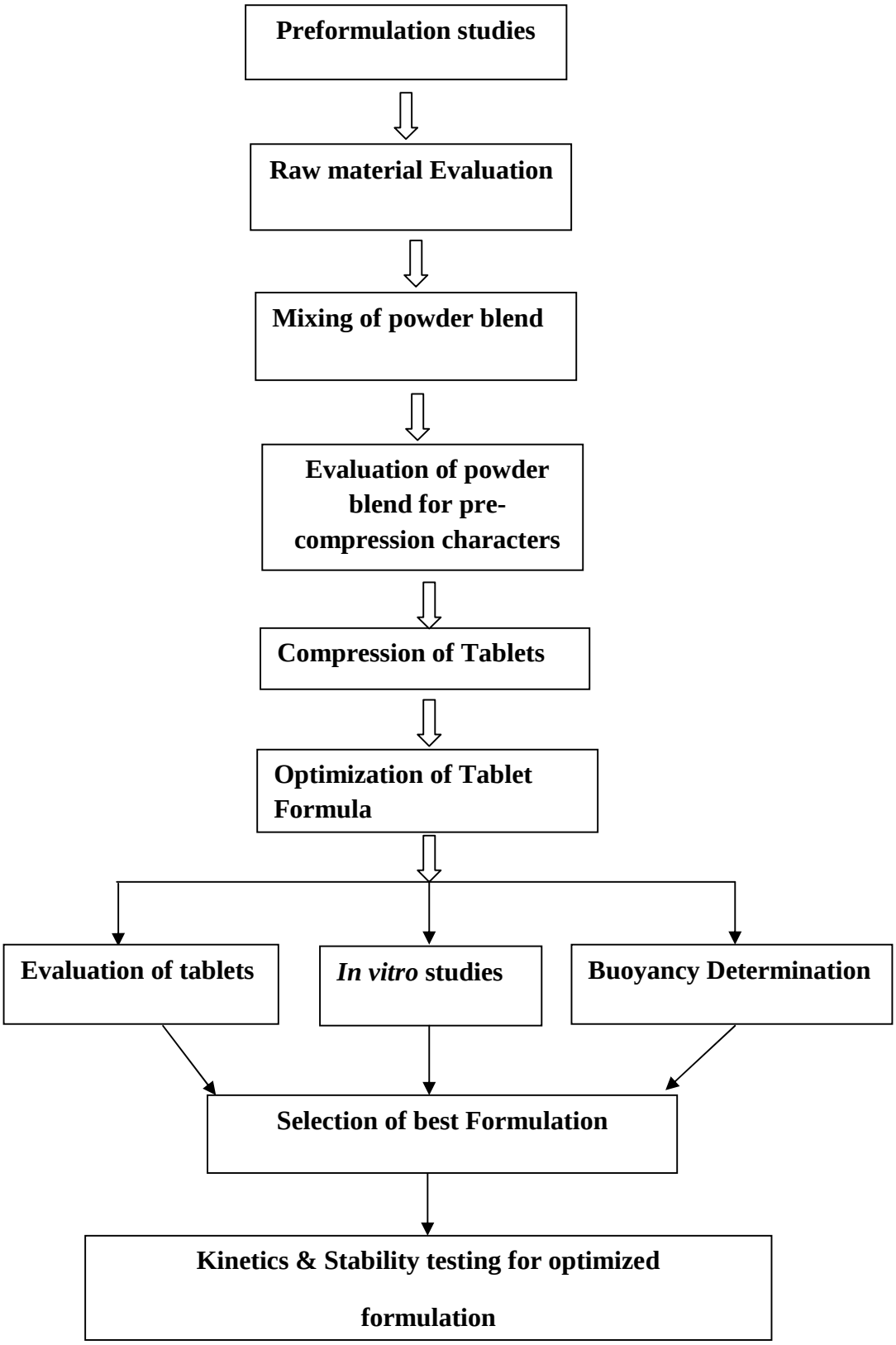
1. Formulation of Losartan potassium floating matrix tablets by direct compression method.
2. Evaluation of Losartan potassium floating matrix tablets
   A. Physical evaluation.
   B. Drug content study.
   C. Swelling study.
   D. Buoyancy study.
   E. Dissolution study.
   F. Kinetic study.

Phase-III:

Stability study of the optimized formulation.

The above given plan of work was presented as flow chart in next upcoming page.

Flow chart of plan of work



DRUG PROFILE

Losartan Potassium

Non Proprietary Name : Losartan Potassium

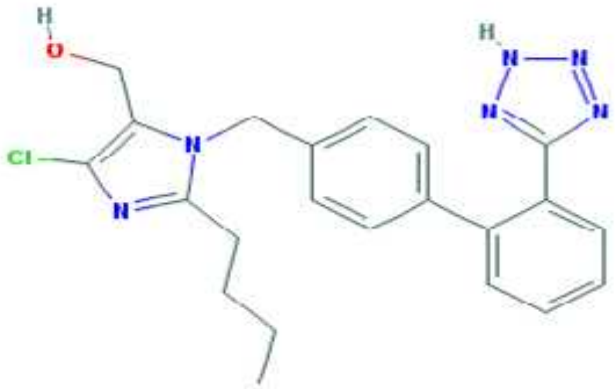
Proprietary name : hyzaar,lacidipine,lortaan

Chemical name :1H-Imidazole-5-methanol,2-butyl-4-chloro-1-[[2(lH-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-,monopotassiumsalt.
2-Butyl-4-chloro-1-[p-(o-lH-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol

Empirical formula : $C_{22}H_{22}ClKN_6O$

Molecular weight : 461 g/mol

Structure:



Physicochemical Profile

Description : losartan is supplied as a crystalline solid.

Solubility : It is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide.

Pharmaceutical Profile

Dosage Forms and dose : it is available as 12.5mg,25, 50 and 100 mg tablets

Pharmacopoeial status : United States Pharmacopoeia

Analytical Profile

Spectrophotometry : Spectrophotometric determination of Losartan potassium in 0.1N HCL with the λ max at 224nm has been reported.

Pharmacokinetic Profile

Oral absorption : It is well absorbed and the systemic bioavailability of Losartan is approximately 33%

Plasma half life : 1.5-2 hours

Protein binding : 99.7%

Pharmacological Profile

Therapeutical category : Anti hypertensive

Mechanism of action

Losartan and its longer acting active metabolite (E-3174) interfere with the binding of Angiotensin II to the Angiotensin II AT1-receptor by, themselves, binding reversibly to the receptors in vascular smooth muscle and the adrenal gland. As Angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance.

Therapeutic/clinical uses

Losartan is used to treat high blood pressure (hypertension) and to protect the kidneys from damage due to diabetes. It is also used to lower the risk of strokes in patients with high blood pressure and an enlarged heart. Lowering high blood pressure helps to prevent strokes, heart attacks, and kidney problems. Losartan belongs to a class of drugs called Angiotensin receptor blockers. It works by relaxing blood vessels so that blood can flow more easily.

Adverse effects :

Adverse effects of losartan have been reported to be usually mild and transient, and include dizziness, headache, and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example those who have received high-dose diuretics). Impaired renal function and rarely rash, urticaria, pruritus, angioedema, and raised liver enzyme values may occur. Hyperkalaemia, myalgia, and arthralgia .

Contraindications:

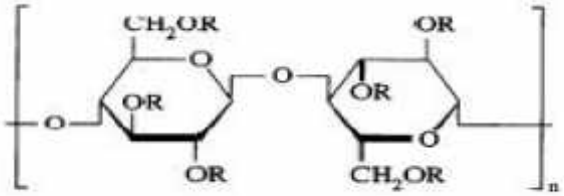
Losartan should not be administered to pregnant women and breast-feeding mothers, because it may disturb the fetal growth or may be harmful to the newborn. It should be cautiously used in patients with renal failure or liver disfunction.

POLYMER PROFILE

HYDROXY PROPYL METHYL CELLULOSE (HPMC)

Synonyms: Methocel, hypromellose.

According to the European pharmacopoeia hydroxypropyl methyl cellulose (hypromellose) is partly o-methylated and o-(2-hydroxypropylated) cellulose.



R: -H, -CH_3 or **-$CH_2CH(CH_3)OH$.**

Hypromellose is an inert, odourless, tasteless, non-ionic, hydrophilic polymer. It is prepared from purified cellulose, which is obtained from cotton linters or wood pulp.

Physicochemical properties of hypromellose:

Solubility, glass transition temperature and viscosity depend upon the ratio of methoxy and hydroxypropoxy groups and the molecular weight. The molecular weight of hypromellose ranges from 10000 to 1500000. Various grades of hypromellose are available which differ in viscosity and extent of substitution. The different grades may be identified by a number indicative of apparent viscosity, in mPa.s, of a 2% aqueous solution at 20°C.The USP identifies hypromellose polymers into four different types according to their relative methoxy-group and hydroxypropoxy-group contents. These are HPMC 1828, HPMC 2208, HPMC 2906, and HPMC 2910. The first two numbers represent the percentage of methoxy groups, the last two numbers the percentage of hydroxypropoxy groups, determined after drying at 105°C for 2hr.

Solubility:

It is practically insoluble in hot water, in absolute ethanol, in acetone, in ether, and in toluene. It dissolves in cold water forming a colloidal solution.

Gel point : 50^0C to 90^0C

pH : 6.0 to 8.0 (1% aqueous solution)

Stability : Very stable in dry conditions, solutions are stable at p^H3.0-11.0. Aqueous solutions are liable to be effected by microbes.

Applications:

- Suspending agent, viscosity modifier, film and matrix forming material.
- Tablet binder and adhesive ointment ingredient

LACTOSE SPRAY DRIED

Synonyms:

FlowLac 100, Lactopress Spray-Dried, NF Lactose–316 Fast Flo, NF Lactose–315, Pharmatose DCL 11, Pharmatose DCL 14, Super-Tab Spray-Dried.

Chemical name:

Spray-dried lactose is a mixture of amorphous lactose, which is a 1 : 1 mixture of α-and-β-lactose, and O-β-D-galactopyranosyl-(14)-α-D-glucopyranose monohydrate.

Empirical Formula and Molecular Weight:

$C_{12}H_{22}O_{11}$: 342.30 (for amorphous)

$C_{12}H_{22}O_{11}$ H_2O :360.31 (for monohydrate)

Functional Category:

Binding agent, directly compressible tablet excipient, tablet and capsule diluents, tablet and capsule filler.

Applications in Pharmaceutical Formulation Technology:

Spray-dried lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting.

Description:

Lactose occurs as white to off-white crystalline particles or powder. It is odourless and slightly sweet-tasting. Spray-dried direct-compression grades of lactose are generally composed of 80–90% specially prepared pure lactose monohydrate along with 10–20% of amorphous lactose.

Method of manufacture:

A suspension of lactose monohydrate crystals in a lactose solution is atomized and dried in a spray drier(2,3) Approximately 10–20% of the total amount of lactose is in solution and the remaining 80–90% is present in the crystalline form. The spray-drying process predominantly produces spherical particles. The compactibility of the material and its flow characteristics are a function of the primary particle size of the lactose monohydrate and the amount of amorphous lactose.

Safety:

Lactose is widely used in pharmaceutical formulations as a diluent in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely due to lactose in tolerance, which occurs in individuals with a deficiency of the enzyme lactase.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material being handled. Excessive generation of dust, or inhalation of dust, should be avoided.

Stability and Storage Conditions

Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

SODIUM BICARBONATE

Synonyms : Sodium hydrogen carbonate, Baking soda, Effer-Soda.

Chemical name: Carbonic acid monosodium salt.

Empirical formula: $NaHCO_3$

Description : Occurs as an odorless, white crystalline powder with a saline taste. The crystalline structure is monoclinic prisms.

Solubility : Soluble in water, practically insoluble in ethanol and ether.

Melting point : 270^0C

Stability and Storage: when heated to about 50^0C, sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate and water. On heating to 250-300^0C for a short time, sodium bicarbonate is completely converted into anhydrous sodium carbonate.

Application in pharmaceutical technology

- Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules in combination with either citric or tartaric acid.
- Buffering agent.
- Therapeutically it is used as an antacid and as a source of the bicarbonate anion in the treatment of metabolic acidosis.
- It is also used as a component of oral rehydration salts. It is used in food products as leavening agent.

MAGNESIUM STEARATE

Synonyms : Magnesium octadecanoate, octadecanoic acid, magnesium salt.

Chemical name : Octadecanoic acid magnesium salt.

Empirical formula: $C_{36}H_{70}MgO_4$

Description:

Magnesium Stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility:

It is practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Melting point:

117-150^{0}C (commercial samples);

126-130^{0}C (high purity magnesium stearate)

Functional category: Tablet and capsule lubricant.

Applications in pharmaceutical formulation or technology:

- Primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.
- It is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is also used in barrier creams.

TALC

Synonyms:

Altalc, hydrous magnesium calcium silicate, hydrous magnesium silicate, purified French chalk, soapstone, steatite, Magsil Star, superior.

Chemical name : Talc

empirical formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Description:

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Stability and Storage conditions:

Talc is a stable material and may be sterilized by heating at 160^0C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Functional Category :

Anti caking agent; glidant; tablet and capsule diluents; tablet and capsule lubricant.

Applications :

- Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent.
- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

6. METERIALS AND METHODS

List of materials and instruments was described in table no 5 and 6

Table 5: LIST OF MATERIALS

S. No	MATERIAL	SUPPLIED BY
1	Losartan	Aurobindo Pharma Limited
2	HPMC K4M	Aurobindo Pharma limited
3	HPMC K15M	Aurobindo Pharma limited
4	HPMCK100M	Aurobindo Pharma limited
5	Lactose	Zeal Chemicals (P) Ltd. Warangal .
6	Talc	Taurus Chemicals (P) Ltd. Secunderabad.
7	Magnesium Stearate	Taurus Chemicals (P) Ltd. Secunderabad.
8	Sodium bicarbonate	Zeal Chemicals (P) Ltd. Warangal.

Table 6: LIST OF INSTRUMENTS

S. No	INSTRUMENTS	MANUFACTURER
1	Electronic balance	Shimadzu ELB-300
2	Sieve no 40	Jaico metals
3	Tablet compression machine	Kimya engineers
4	Tablet hardness tester	Monsanto
5	Friability test apparatus	Roche Friabilator
6	Tablet dissolution tester	Lab India
7	Bulk density apparatus	Keetan&company
8	Stability control oven	Biotechno lab, BTL
9	UV-Visible spectrophotometer	Lab India, Lambda 25
10	FTIR spectrophotometer	Bruker Alpha-T

6.1 PRE-FORMULATION STUDIES:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such the appropriate physical, chemical data is available to aid the selection of new chemical entities that enter the development processed during this evaluation possible interaction with various inert ingredients intended for use in final dosage form were also considered in the present study.

The following pre-formulation studies were performed:

- Study of organoleptic properties
- Solubility analysis
- Melting point of drug
- Drug powder characterization
- Physical compatibility studies
- Identification of drug-excipients compatibility study by FT-IR

6.1.1 Organoleptic properties:

The Organoleptic character of the drug like colour, odour, taste and appearance play an important role in the identification of the sample and hence they should be recorded in an descriptive terminology.

6.1.2 Solubility Studies

It is important to know about solubility characteristics of a drug in aqueous systems, since they must posses some limited aqueous solubility to elicit a therapeutic response. Quantitative determination of solubility was made by preparing saturated solution of drug in a constant volume of pH 1.2, 6.8, 7.4 phosphate buffers and resulting solutions were kept at room temperature for 24 hours with intermediate

shaking. The resulting solutions were filtered and analyzed for dissolved drug by U.V spectrophotometry at λmax of 224 nm.

6.1.3 Melting point:

The melting point of Losartan potassium was determined by capillary method, using small quantity of Losartan potassium is taken and placed in apparatus and determined the melting point and matched with standards.

6.1.4 Loss on drying:

Determined 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. Accurately weighed the substance to be tested. If the sample was in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the sample in bottle, replace the cover and accurately weighed the bottle and the contents. By gentle, sidewise shaking, distribute the sample as evenly as practicable to a depth of about 5 mm. Place the loaded bottle in the drying chamber. Dried the sample at the specified temperature from constant weight. Upon opening the chamber, close the bottle promptly and allow it to come to room temperature in desiccators before weighing.

The difference between successive weights should not be more than 0.5mg. The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

6.1.5 Drug powder characterization:

6.1.5.1 Angle of repose: Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area and co-efficient of friction of the raw material.

Method: Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend was allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\Theta = \tan^{-1} (h/r)$

Where, h = height of heap, r = radius of heap, Θ = angle of repose.

Table 7: Limits:

Angle of repose	**Flow property**
$<25^{o}$	Excellent
$25\text{-}30^{o}$	Good
$30\text{-}40^{o}$	Passable
$>40^{o}$	Very poor

6.1.5.2 Bulk density: Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density is increased. In addition as the granule size increases bulk density decreases.

Method: weighed quantity of active powder ingredient (API) was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by the API was measured. Bulk density was measured by using the formula

Bulk Density = Bulk Mass / Bulk Volume

6.1.5.3 Tapped density: Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes is observed the mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weigh a specific distance. Device that rotates device during tapping may be preferred to minimize any possible separation of the mass during tapping down.

Cylinder dropping distance: 14± 2mm at a normal rate of 300 drops / minute.

Unless otherwise specified, tab the cylinder 500 times initially and measure the tapped volume Va, the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, Vb, to the nearest graduated unit. If the difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf . Repeat in increments of 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula:

$$\text{Tapped Density} = \frac{m}{Vf}$$

Where, m = initial weight of material in gm,

Vf = volume of material after tapping.

Generally replicate determinations are desirable for the determination of this property.

6.1.5.4 Measurement of Powder Compressibility:

The compressibility Index and Hausner's ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These

differences are reflected in the compressibility Index and the Haussler ratio which was calculated by the following formula:

Compressibility index*:* = $100\frac{(V_0 - Vf)}{V_0}$

Where, Vf = final tapped volume, Vo = initial un tapped volume.

Table 8: Limits

S.no	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Verypoor
6	>40	Extremelypoor

Hausner's ratio: = $\frac{V_0}{Vf}$

Where, Vf = final tapped volume, Vo = initial un tapped volume.

Table 9: Limits

S.No	Hausner's ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

6.1.5.5 Physical compatibility studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients, the latter could affect the stability of the drug. Knowledge of drug excipient interactions, therefore very useful to the formulator in selecting the appropriate excipients.

Losartan potassium was mixed well with the excipients according to the formula selected for the tabletting and kept small portion of this mixed powder in cleaned and dried vials in stability chamber at $40^{o}C \pm 2^{o}$ C / 75±5RH and room temperature. Physical observations have been carried out visually for 7 days

6.2 Drug-Excipient Compatability Studies

6.2.1 Fourier Transform Infrared (FTIR) Spectroscopy

The Infrared spectra of samples were obtained using by infrared spectrophotometer. Pure drug, excipients, physical mixture of drug and excipients were subjected to FTIR study. The IR spectra were obtained using KBr disk method

6.3 Construction of calibration curve

6.3.1 Standard graph of Losartan potassium in 0.1N HCl

The stock solutions were freshly prepared by dissolving 100mg of Losartan in a 100ml volumetric flask and then made up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/ml (stock I). 10ml of this solution was diluted to 100ml with 0.1N HCl to obtain a solution of strength 100 µg/ml (stock II). From this secondary stock required concentrations 2, 4, 6, 8, 10, 12 and 14 µg/ml is prepared. The absorbance was measured at 224 nm using a UV Spectrophotometer.

6.4 Formulation of floating matrix tablets of Losartan potassium:

The key ingredients included in the formulation are:
Hydrophilic polymers: HPMC K4M, HPMC K15M, and HPMC K100M
Effervescent agent : Sodium carbonate
Filler : Lactose
Anti adherent : Talc
Lubricant : Magnesium Stearate

Accurately weighed quantities of polymer and lactose were taken in a mortar and mixed geometrically to this required quantity of Losartan was added and mixed with the pestle. Accurately weighed quantity of sodium bicarbonate was then mixed with the drug blend. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine using 10-mm standard flat-face punches.

Table10: Composition of floating matrix tablets of Losartan potassium

Ingredient (mg)	Composition(mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Losartan potassium	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	75	100	125	-	-	-	-	-	-	50	-	50
HPMC K15M	-	-	-	75	100	125	-	-	-	50	50	-
HPMC K100M	-	-	-	-	-	-	75	100	125	-	50	50
$NaHCO_3$	50	50	50	50	50	50	50	50	50	50	50	50
Lactose	172	147	122	172	147	122	172	147	122	147	147	147
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total wt (mg)	300	300	300	300	300	300	300	300	300	300	300	300

6.5 Evaluation of floating matrix tablets of Losartan potassium

6.5.1 Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using vernier callipers.

6.5.2 Hardness

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this six tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

6.5.3 Friability

The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. Here twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations i.e., 25 rpm for 4 minutes, the tablets were again weighed (w). The percent loss in weight or friability (F) is calculated by the formula

$$F= (1-W/Wo) \times 100$$

F= friability

Wo= initial weight

6.5.4 Weight variation

This test was performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This was done by sampling randomly and weighing 20 tablets and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage show in the table 11 and none deviate by more than twice the percentage. The mean and standard deviation were determined.

Table 11: Pharmacopoeial specifications for tablet weight variation

Average weight of tablets (mg) (I.P)	Average weight of tablets (mg) (U.S.P)	± % deviation allowed
Less than 80	Less than 130	10
80 – 250	130 – 323	7.5
More than 250	More than 324	5

6.5.5 Content Uniformity

This test was performed to maintain the uniformity of weight of active ingredient in each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. This test was performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet equal to 100 mg of losartan is dissolved in 0.1 N HCL in 100ml volumetric flask. It is diluted and the absorbance is measured at 224 nm using 0.1 N HCL as blank and the % drug content was estimated using the following formula.

$$\text{Concentration (mcg/ ml)} = \frac{\text{Absorbance-intercept}}{\text{Slope}}$$

Drug content (mg) = concentration x dilution factor

$$\%\ \text{Drug content} = \frac{\text{Drug content (mg)}}{\text{Label claim (mg)}} \times 100$$

6.6 In vitro buoyancy determination

The floating characteristics of the GFDDS are essential, since they influence the *in vivo* behaviours of the drug delivery system. However there seemed to be no threshold value for the floating system to remain a float under a physiological condition due to the latter's complication.

6.6.1 Floating Lag Time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium at pH 1.2, temperature 37 ± 0.5˚C, paddle rotation at 50 rpm.

6.6.2 Total Floating Time: The time taken by the tablet to float constantly on the surface of the gastric fluid , at pH 1.2, temperature 37 ± 0.5˚C, paddle rotation at 50 rpm.

6.6.3 Buoyancy / Floating Test:

The *in vitro* buoyancy was determined by floating lag time, as per the method described by a Rosa *et al.*,1994. Here, the tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

6.6.4 Water uptake studies:

The swelling behaviour of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at $37^{o}\pm 0.5^{o}$c, rotated at 50 rpm. At selected regular intervals the tablet is withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU)(Chavanpatil et al., 2006).

%WU = (Wt - Wo) * 100 / Wo

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet.

6.7 In vitro dissolution studies

Dissolution studies were carried out using USP II dissolution apparatus. The stirring speed was 50 rpm. 0.1 N hydrochloric acid is used as dissolution medium (900ml). It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed at 224 nm by using a double beam UV spectrophotometer. Each dissolution study is performed three times and the mean values were taken.

6.8 Kinetic model fitting:

To analyze the *in vitro* release data and to determine the release mechanism various kinetic models were used. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

There are several linear and non-linear kinetic models to describe release mechanisms (Higuchi, Peppas model) and order of release(Zero and First order).

- Zero order kinetics
- First order kinetics
- Korsmeyer-Peppas model
- Higuchi model

6.8.1 Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant. Dividing this equation by W_0 and simplifying

$$f_t = k_0 t$$

Where $f_t = 1 - (W_t / W_0)$ and f_t represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant in this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were filled. In this way a graphical relationship between f_t versus time to get the Zero order constant from the slope. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems as well as matrix tablets with low soluble drugs (Varelas *et al.,* 1995), coated forms, osmotic systems, etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

6.8.2 First order kinetics

This type of model to analyze drug dissolution study is first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model

$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$

Where Q_t is the amount of drug released in time t, Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant. In this way a graphical relationship between log percent drug remaining versus time to get the first order constant from the slope. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices release the drug in a way that is proportional to the amount

of drug remaining in its interior, in such a way, that the amount of drug released by unit of time diminishes.

6.8.3 Korsmeyer Peppas model (power law)

Korsmeyer et al., (1983) developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t)

$Q_t/Q_\alpha = K_k t^n$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism. For matrix tablets, an n value of <0.5 indicates diffusion – controlled mechanism while an n value of <1.0 indicates erosion (Ford et al., 1991). Hariharan *et al.,* 1997 a suggested that if the value of n is 0.5, it indicates Fickian transport, a value of 0.5 and 1.0 non-Fickian transport, and the values close to 1.0 indicate that the system is releasing drug in a zero-order manner regardless of the actual mechanism of release.

Table 12: Release Mechanism –Korsmeyer Peppas Kinetic Model

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport or non-Fickian	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

This type of analysis of release behaviour is valuable to the formulator for comparative purposes (Hariharan et al., 1997b). The Release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t. This model is used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon being involved.

6.8.4 Higuchi Model (Higuchi 1961, Higuchi 1963)

$$Q_t = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and

K_H = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus the concentration indicates that the drug release follows strict Fickian diffusion. For purpose of data treatment, the above equation is usually reduced to:

$$Q = Kt^{1/2}$$

Therefore a plot of amount of drug released versus the square root of time should be linear if drug release from the matrix is diffusion controlled. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time. An important advantage of the above equations is its simplicity.

The following plots were made using the in-vitro drug release data:

- Cumulative % drug release vs. time (Zero order kinetic model);
- Log cumulative of % drug remaining vs. time (First order kinetic model);
- Cumulative % drug release vs. square root of time (Higuchi model);
- Log cumulative % drug release vs. log time (Korsmeyer – Peppas model).

6.9 Stability protocol:

The purpose of stability testing is to provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-testing for the drug substances or a shelf-life for the drug product and recommended storage conditions.

The storage conditions used for stability studies were accelerated conditions (40°C±2°C/75%±5% RH).Stability study was carried out for the optimized formulation. Tablets of optimized formulation were striped packed and kept in stability chamber for 3 months on above mention temperature.

Test Performed:

- Test for other physical parameters.
- Dissolution profile.

7. RESULTS AND DISCUSSIONS

7.1 PRE-FORMULATION STUDIES

7.1.1 Organoleptic properties

Table 13**: Observation of organoleptic properties:**

TEST	SPECIFICATION	OBSERVATION
Colour	White or almost white powder	White powder
Odour	---	Odourless

7.1.2 Solubility analysis

Losartan potassium samples are examined and it was found to be soluble in water and phosphate buffer pH 1.2, 6.8and 7.4.

7.1.3 Melting point of drug

The melting point of Losartan potassium was determined by capillary method, melting point of Losartan potassium was found to be 184°C. Melting point compared with USP standards that showed that drug was pure.

7.1.4 Loss of Drying

It was determined as per procedure given in methodology. The results were as follows

Table 15: Observations for loss on drying

Test	Loss on drying	Observation
Loss on drying	Not more than 0.5%	0.41%

The loss drying of drug was founded as0.41 which was within the limit.

7.1.5 Drug powder characterization:

7.1.5.1 Angle of repose

It was determined as per procedure given in material and methodology section.

Table 14: Determinations of Angle of repose

Material	**Angle of repose**
Losartan potassium Raw material	24°56"

The results indicating that the raw material has good flow property.

7.1.5.2 Flow properties

The method to determine the flow properties are given in methodology.

Table 16: Flow properties of pure drug

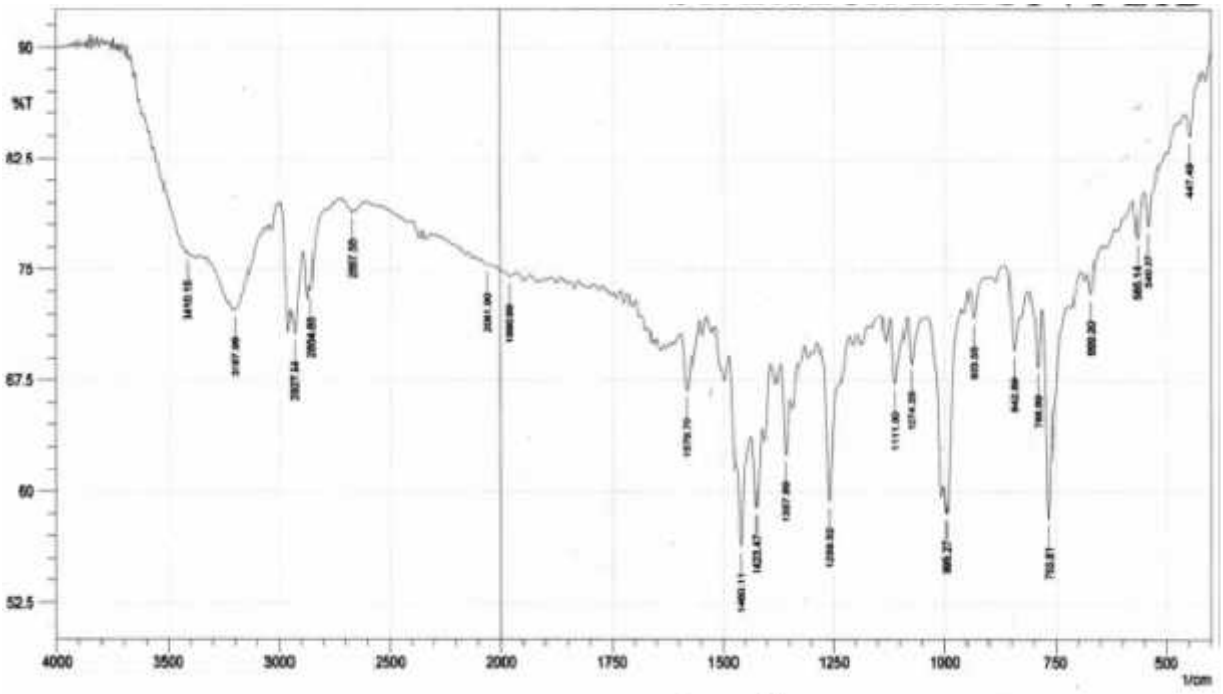
Material	**Bulk density**	**Tapped density**	**Carr's index (%)**	**Hausner's ratio (%)**
Losartan potassium raw material	0.347±0.04	0.391±0.07	15.52±0.01	1.19±0.06

The results are clearly indicating that the Losartan potassium raw material has good flow and cohesive nature.

7.2 FTIR Studies

Potential chemical interactions between the drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibilities of chemical interaction between drug and excipients. FTIR spectra of pure drug and optimized formulations were analyzed over the range 400-4000cm-1. (shown in Figure 10 to 15) the IR spectrum of pure Losartan potassium showed strong absorption bands at wave numbers of 3195, 2957, 1460, 1423, 1260 , 995.8,and763.7cm-1. Due to hydroxyl stretching--- OH, C—H, C=0 stretching, N-H bending, C-H bend in plane and C-C stretching respectively in optimized formulations also these peaks were well preserved with additional peaks which correspond to the excipients used in the formulation. This indicates no drug-excipient interaction

Figure 10: FTIR spectra of pure drug, Losartan potassium



wave number cm^{-1}

Figure 11: FTIR spectra of HPMC

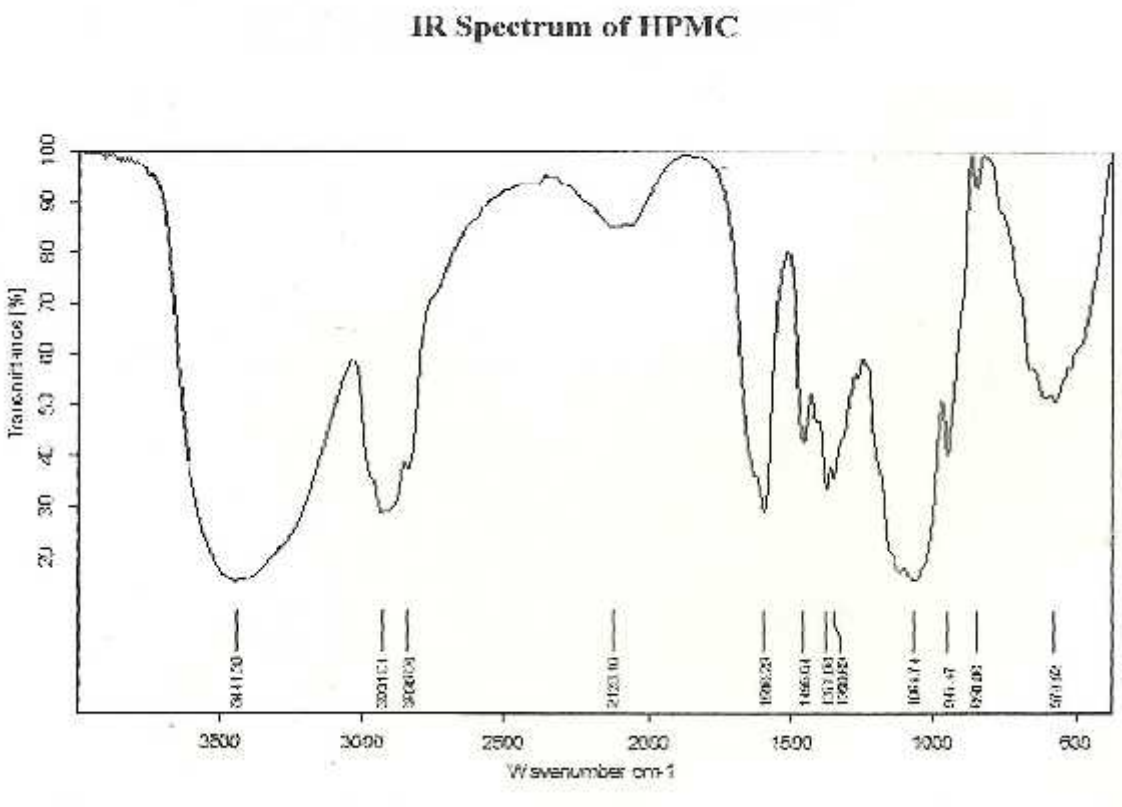


Figure 12: FTIR spectra of LACTOSE

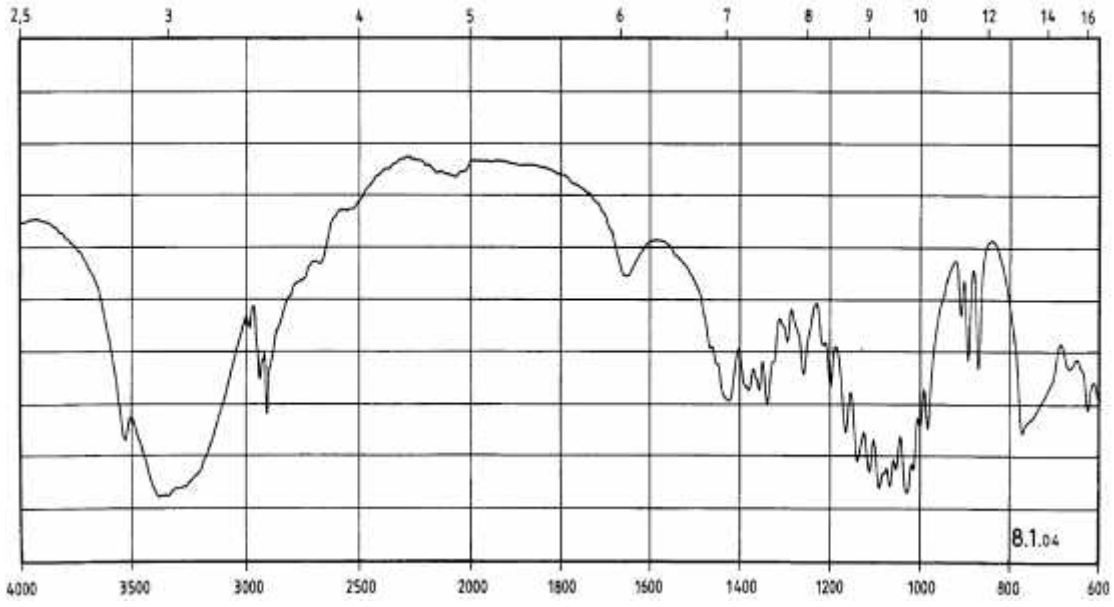


Figure 13: FTIR spectra of Mg.stearate

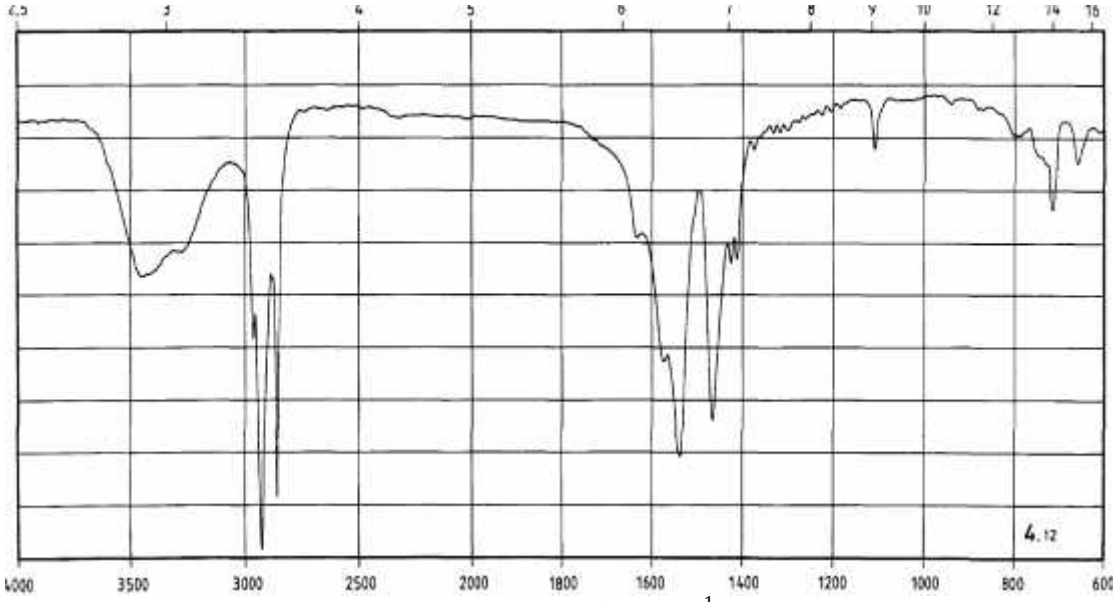


Figure 14: FTIR spectra of Talc

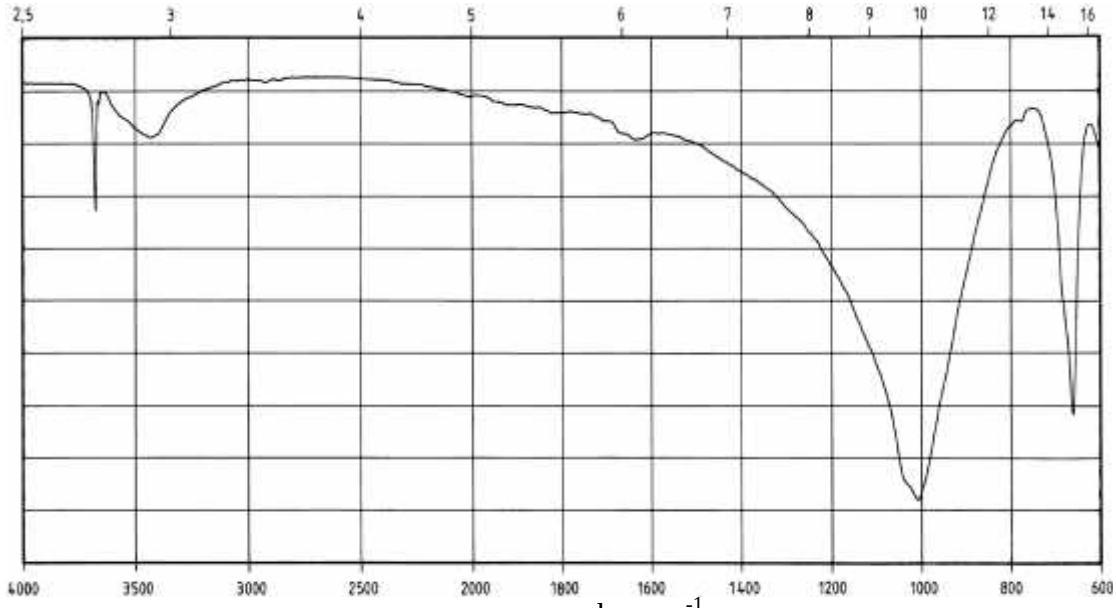
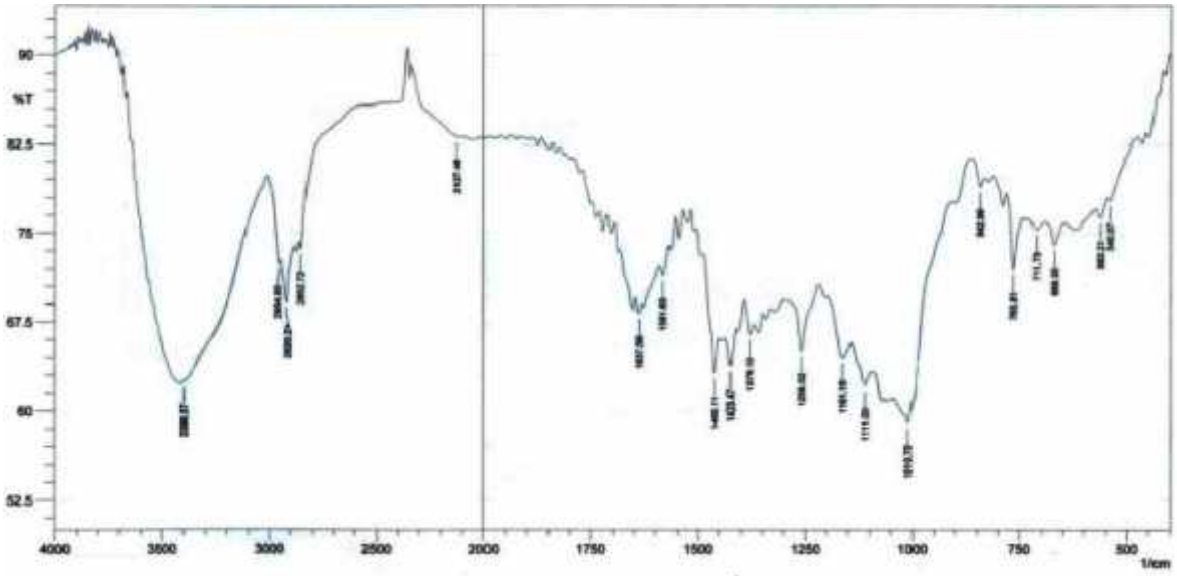


Figure 15 : FTIR spectra of pure drug and polymers



wave number cm^{-1}

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S. No	Functional Group	Observed Value (cm^{-1})	Theoretical value (cm^{-1})
1	C-H stretching	763.05	1000-675
2	O-H stretching	995.29	1050-1150
3	C-N stretching	1260.47	1340-1020
4	C-O stretching	1423.10	1250-1350
5	C=C stretching	1460.23	1450-1600
6	N-H bending	2957.64	2500-3000
7	C-H bending	3195.36	3500-4000

Peaks were well preserved with additional peaks which correspond to the excipients used in the formulation. This indicates no drug-excipient interaction

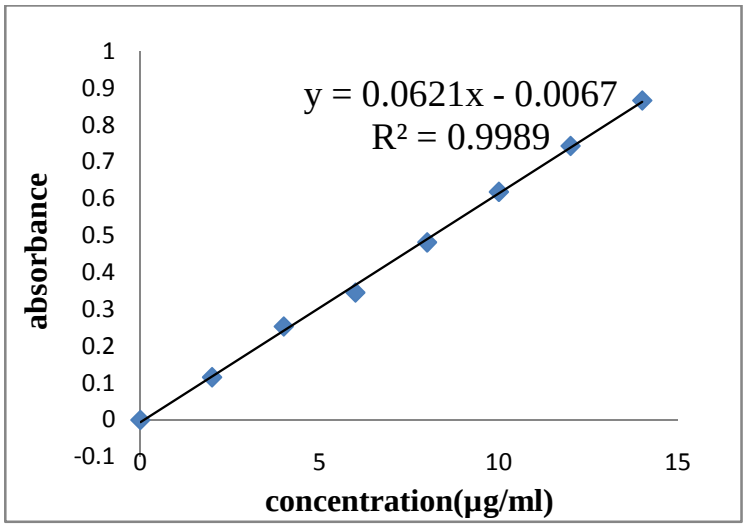
7.3 Standard graph of Losartan in 0.1N HCL

The scanning of the volumetric solution of Losartan in the ultraviolet range (200-400nm) against 0.1 N HCL blank gave the λ_{max} as 224 nm. The standard concentrations of Losartan (2-14 µg/ml) prepared in 0.1N HCL showed good linearity with R^2 value of 0.9989, which suggests that it obeys the Beer-Lamberts law.

Table19: Absorbance of Losartan potassium of different concentrations at λ_{max} (224nm).

Concentration(µg/ml)	Absorbance
0	0
2	0.1158
4	0.2535
6	0.3458
8	0.4819
10	0.619
12	0.7436
14	0.867

Figure16: Standard graph of Losartan potassium in 0.1N HCL



7.4 EVALUVATION OF PRECONPRESSION PARAMETERS

The following parameters were carried out by the procedure given in 6.1.5.1. The results were illustrated in the below table.

Formulation code	Angle of repose (degree± SD)	BD (gm/ml± SD)	TD (gm/ml± SD)	Carr's index (%± SD)	Hausner's ratio (%± SD)
F1	24.12±0.04	0.317±0.01	0.367±0.02	14.65±0.06	1.08±0.05
F2	23.07±0.01	0.327±0.03	0.389±0.04	15.21±0.07	1.09±0.04
F3	26.04±0.03	0.337±0.06	0.381±0.01	13.63±0.04	1.11±0.02
F4	25.0i±0.07	0.347±0.04	0.391±0.07	16.52±0.01	1.19±0.06
F5	22.97±0.09	0.296±0.03	0.320±0.03	13.12±0.03	1.16±0.03
F6	25.71±0.06	0.260±0.01	0.336±0.01	15.27±0.01	1.15±0.01
F7	24.16±0.03	0.266±0.04	0.372±0.02	14.56±0.04	1.16±0.03
F8	21.11±0.09	0.307±0.05	0.332±0.03	13.41±0.07	1.17±0.05
F9	26.16±0.04	0.312±0.02	0.356±0.01	16.31±0.05	1.18±0.04
F10	26.04±0.03	0.347±0.04	0.381±0.01	13.63±0.04	1.11±0.02
F11	25.0i±0.07	0.296±0.03	0.391±0.07	16.52±0.01	1.19±0.06
F12	22.97±0.09	0.260±0.01	0.320±0.03	13.12±0.03	1.16±0.03

7.4.1 Physical compatibility test

The method for determination of physical compatibility test was given in methodology.

Table 17: Observation for physical compatibility test

Test	Observation	Inference
Description	No colour change was observed	Complies with the condition

The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

7.5 Evaluation of physical parameters of floating matrix tablets of Losartan potassium

All the prepared formulations were tested for physical parameters like Hardness, Thickness, Weight variation, Friability, Total floating time, Floating lag time are fond to be within pharmacopeias limits. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicates that prepared formulations were good.

Table 20: Physical parameters of floating matrix tablets of Losartan potassium.

Batch No	Tablet Thickness (mm)	Weight Variation(mg)	Hardness Kg/cm^2	Drug content (%)	Friability (%)	Lag time (sec)	Total floating time(sec)
F1	3.52±0.05	350±7.2	4.0±0.4	98.78±1.2	0.44	65	>12
F2	3.53±0.07	350±8.3	4.1±0.3	97.6±0.98	0.45	68	>12
F3	3.55±0.06	352±7.1	4.06±0.6	96.6±0.43	0.36	70	>12
F4	3.53±0.03	352±9.4	4.02±0.4	93.3±1.43	0.51	80	>12
F5	3.51±0.08	351±7.8	4±0.2	86.6±0.56	0.52	73	>12
F6	3.52±0.04	350±9.4	4.3±0.2	99.9±1.43	0.27	70	>12
F7	3.56±0.07	351±8.6	4.0±0.2	98.1±0.97	0.37	52	>12
F8	3.55±0.05	349±11.6	4.3±0.3	101±1.03	0.38	45	>12
F9	3.51±0.05	349±10.5	4.0±0.2	99.3±1.02	0.42	45	>12
F10	3.59±0.05	349±9.2	4.2±0.5	99.3±1.32	0.45	75	>12
F11	3.53±0.08	352±1.4	4.2±0.2	97.37±2.6	0.45	55	>12
F12	3.58±0.05	351±8.6	4.1±0.5	97.5±2.31	0.43	70	>12

All values represent mean ± standard deviation (SD) n=3.

7.6 SWELLING STUDIES:

Table 21: Percent swelling of formulations with HPMC K4M and K15M

Sampling time(hr)	F1	F2	F3	F4	F5	F6
1	15.41	21.83	23.53	16.97	22.87	22.45
2	19.96	34.33	37.65	22.47	35.73	36.42
3	42.19	52.33	56.63	48.34	53.68	54.66
4	60.22	71.26	75.64	69.19	72.34	78.76
6	79.89	84.74	88.78	81.83	90.42	99.38
8	68.26	79.28	80.27	79.59	82.69	88.14
10	61.15	72.36	76.85	76.02	76.93	82.64
12	59.35	68.48	71.36	70.99	73.29	78.54

All values represent mean ± standard deviation (SD) n=3.

Figure17.Percent swelling of formulations with HPMC K4M&K15M

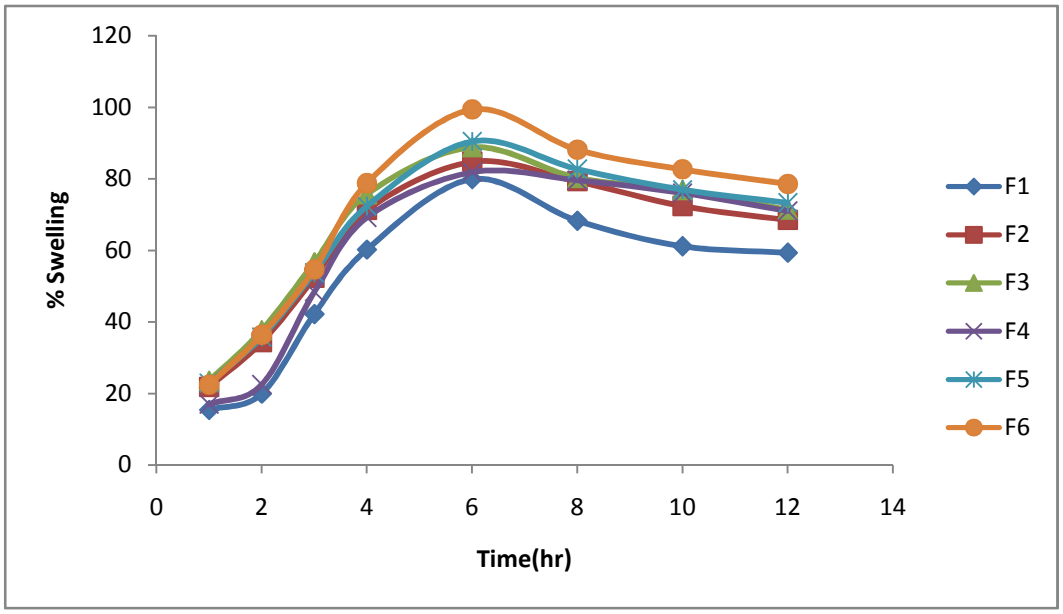
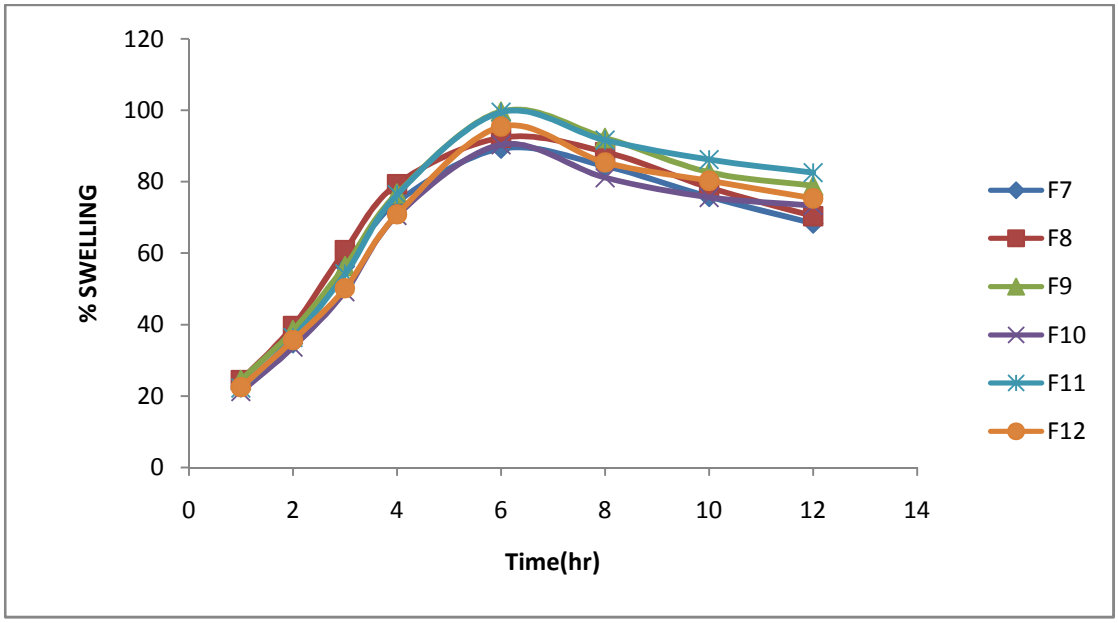


Table 22: Percent swelling of formulations with HPMC K100M and polymer combinations

Sampling time(hr)	F7	F8	F9	F10	F11	F12
1	22.56	24.45	24.48	21.27	22.26	22.47
2	34.73	39.57	38.46	33.76	36.38	35.64
3	56.26	60.84	56.37	49.27	54.18	50.15
4	74.28	79.36	76.72	70.56	76.45	70.84
6	89.27	92.34	99.64	90.36	99.48	95.42
8	84.38	88.34	92.27	81.16	91.65	85.37
10	75.74	78.38	82.64	75.64	86.24	80.25
12	68.34	70.37	78.84	73.34	82.56	75.32

All values represent mean ± standard deviation (SD)

Figure18: Percent swelling of formulations with HPMC K100M& combination of polymers



The percentage swelling obtained from the water uptake studies of the formulations was shown in tables 21 and 22. The floating tablets containing HPMC K4 , K15M and K100m showed higher percent swelling up to the first 6^{th} hour but could not maintain their matrix integrity up to 12 h. The floating tablets containing HPMC K4M (F1 to F3) showed less percentage of swelling when compared with HPMC K15M and HPMC K100M. The floating tablets containing HPMC K15M showed less amount of swelling when compared with HPMC K100M This was due to increase in the viscosity of polymer, the swelling increases more and the drug release will be decreased. So formulations containing HPMC K100M showed more amount of swelling when compared with the other formulations. From the above figures we can observe that formulations containing HPMC K100M has more swelling properties from the other two polymers.

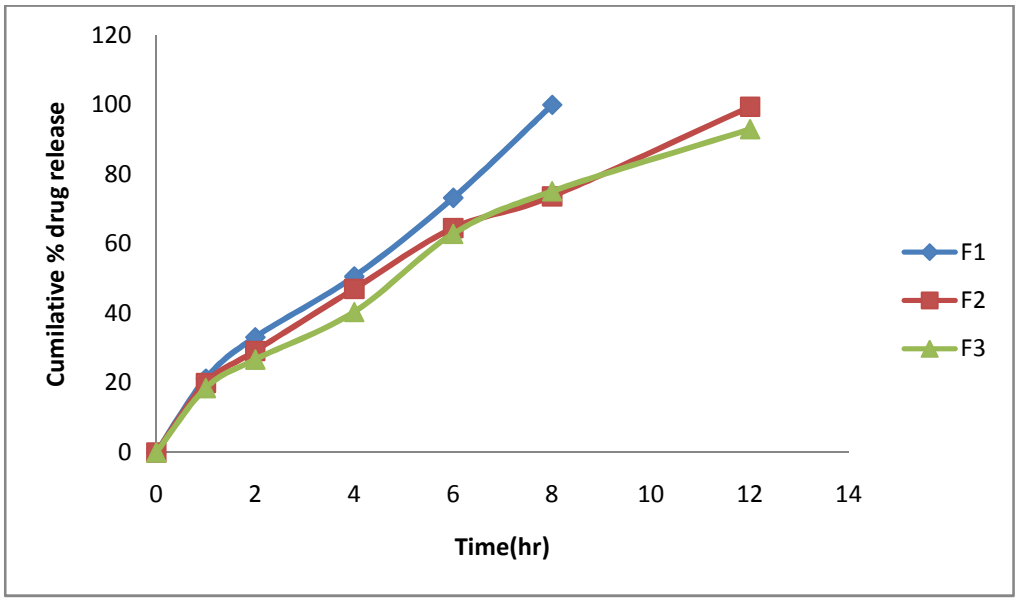
7.7 *IN VITRO* DRUG RELEASE STUDY:

Table 23: Cumulative Percentage drug release of formulations with HPMC K4M (F1, F2, F3)

S. No	Time(hrs)	F1	F2	F3
1	0	0	0	0
2	1	21.22	19.97	18.50
3	2	33.13	29.13	26.70
4	4	50.56	47.00	40.36
5	6	73.18	64.46	62.83
6	8	99.91	73.61	75.07
7	12	-	99.33	92.88

All values represent mean ± standard deviation (SD) n=3.

Figure 19: Cumulative percentage drug release of formulations containing HPMC K4M



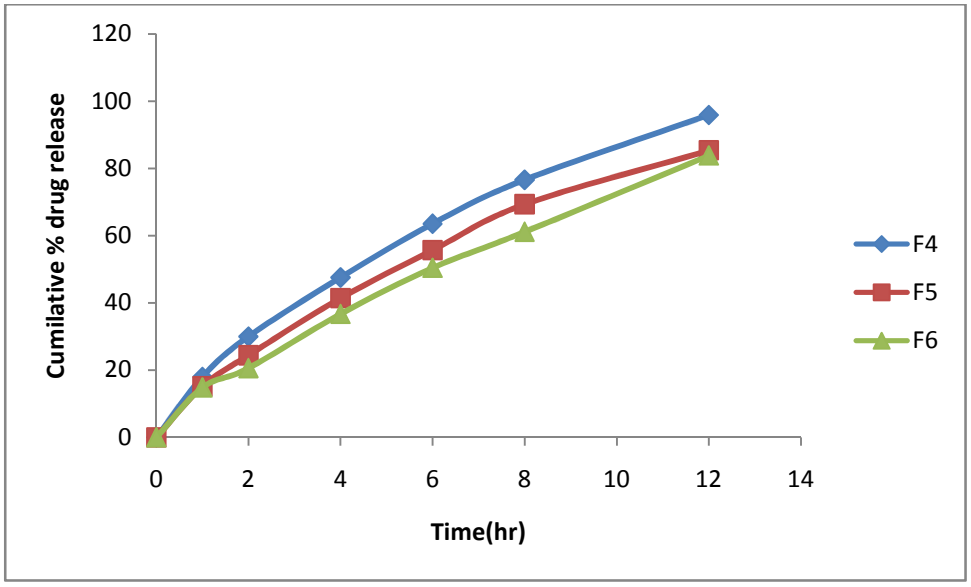
From the above figure it can be observed that the polymer HPMC K4M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F1, F2 and F3 was 99.91, 99.33, 92.88 respectively and difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. Formulations F1 failed to release the drug within the desired time. Formulation F2 and F3 release drug from floating matrix above 12 hr. Formulation F2 was considered as best formulation among all three formulations it showed good buoyancy properties (floating lag time: 78 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

Table 24: Cumulative percentage drug release of formulations with HPMC K15M

S. No	Time(hrs)	F4	F5	F6
1	0	0	0	0
2	1	17.98	15.17	14.83
3	2	29.98	24.41	20.57
4	4	47.55	41.41	36.70
5	6	63.52	55.66	50.41
6	8	76.57	69.32	61.12
7	12	95.84	85.33	83.81

All values represent mean ± standard deviation (SD) n=3.

Figure21: Cumulative percentage drug release of formulations containing HPMC K100M



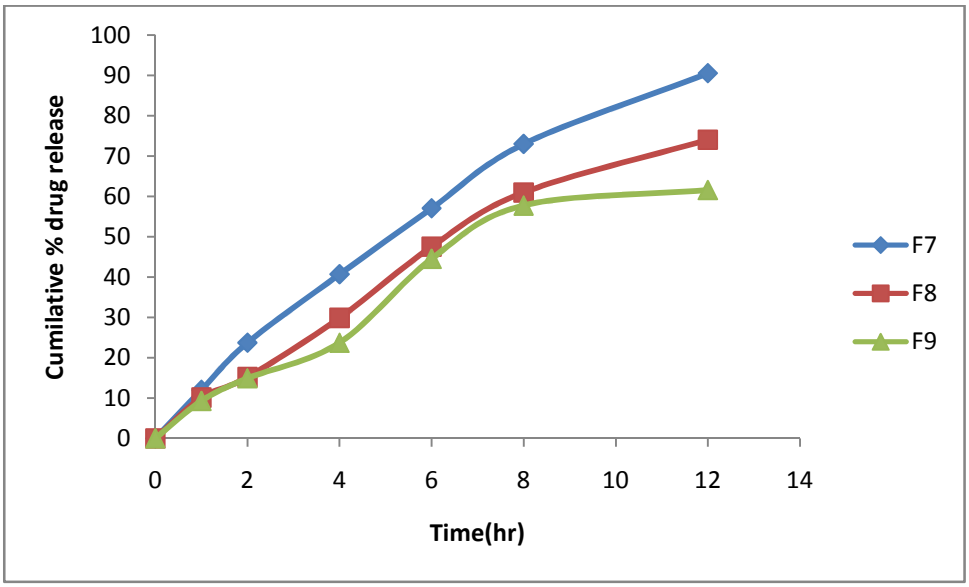
From the above figure it can be observed that the polymer HPMC K15M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F4, F5, and F6 95.84, 85.33 and 83.81 in 12 h respectively . Formulations F6, F7 and F8 failed to release the drug within the desired time. The difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. All these three formulations floated for 12h. Formulation F4 was considered as best formulation among all four formulations it showed good buoyancy properties (floating lag time: 80 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

Table25: Cumulative percentage drug release of formulations with HPMC K100M

S. No	Time(hrs)	F7	F8	F9
1	0	0	0	0
2	1	11.99	10.10	9.29
3	2	23.71	15.17	14.89
4	4	40.68	29.87	23.71
5	6	57.02	47.52	44.52
6	8	72.97	60.95	57.72
7	12	90.47	74.01	61.55

All values represent mean ± standard deviation (SD) n=3.

Figure21: Cumulative percentage drug release of formulations containing HPMC K100M



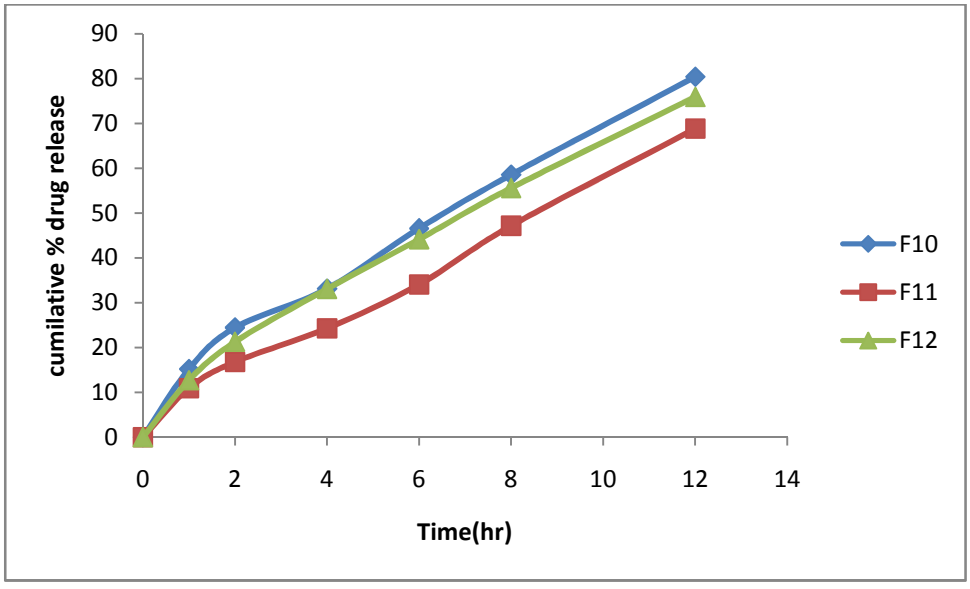
` From the above figure it can be observed that the polymer HPMC K100M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F7, F8 and F9 are 90.47, 74.01 and 61.55 in 12 h respectively. Formulations F8 and F9 failed to release the drug within the desired time. The difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. All these three formulations floated for 12h. Formulation F7 was considered as best formulation among all three formulations it showed good buoyancy properties (floating lag time: 52 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

Table 26: Percent drug release of formulations with combination of polymers

S. No	Time(hrs)	F10	F11	F12
1	0	0	0	0
2	1	15.20	10.94	12.69
3	2	24.43	16.79	21.26
4	4	33.11	24.29	33.08
5	6	46.56	34.07	44.13
6	8	58.53	47.18	55.57
7	12	80.36	68.84	75.86

All values represent mean ± standard deviation (SD) n=3.

Figure 22: Cumulative % drug release of formulations containing combination of polymers



From the above figure it can be observed that the polymer HPMC K4M, K15M and K100M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F10, F11, and F12 was 80.36, 68.84, and 75.86 in 12 h respectively. These are the formulations done by combination of polymers. Formulations F11,and, F12, failed to release the drug within the desired time and difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer and due to the high viscosity of the polymers. The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in table 16 and 20 respectively. Formulation F10 was considered as best formulation among all three formulations it showed good buoyancy properties (floating lag time: 75 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in tables 23 to 26 respectively. Fomulation F2 showed good drug release and buoyancy time than all other formulations. The formulation F2 showed a constant release in a controlled manner with 99.33%. Hence F2 was chosen for kinetics studies.

7.8 DRUG RELEASE MECHANISM:

7.8.1 RELEASE KINETICS

Table 27: Release kinetics of the optimum formulation F2

S.no	Time (hr)	√T	Log T	Cumulative %drug dissolved	Cumulative %drug un dissolved	Log Cumulative %drug dissolved	Log Cumulative %drug un dissolved
1	0	0	0	0	100	0	2.0
2	1	1.0	0	19.97	80.03	1.03	1.903
3	2	1.414	0.30	29.13	70.87	1.46	1.85
4	4	2.0	0.60	47.00	53.00	1.67	1.72
5	6	2.4	0.778	64.46	35.54	1.809	1.55
6	8	2.8	0.90	73.61	26.39	1.867	1.42
7	12	3.16	1.0	99.33	0.67	1.99	-0.17

Figure 23: Zero order plot (F2) Formulation

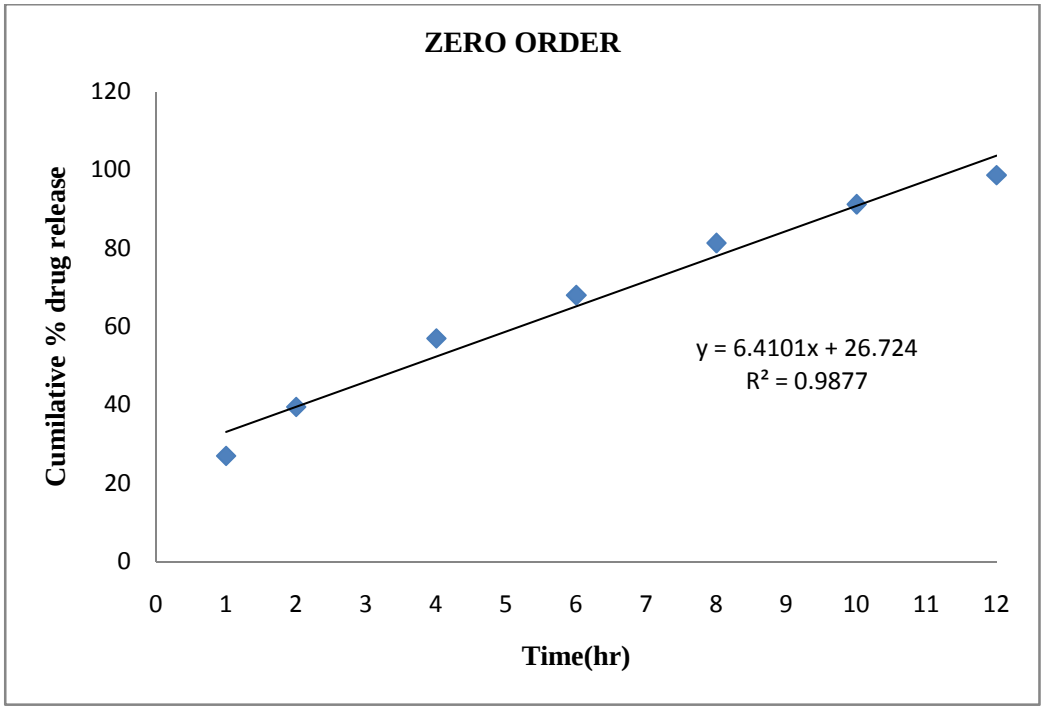


Figure 24: First order plot (F2)

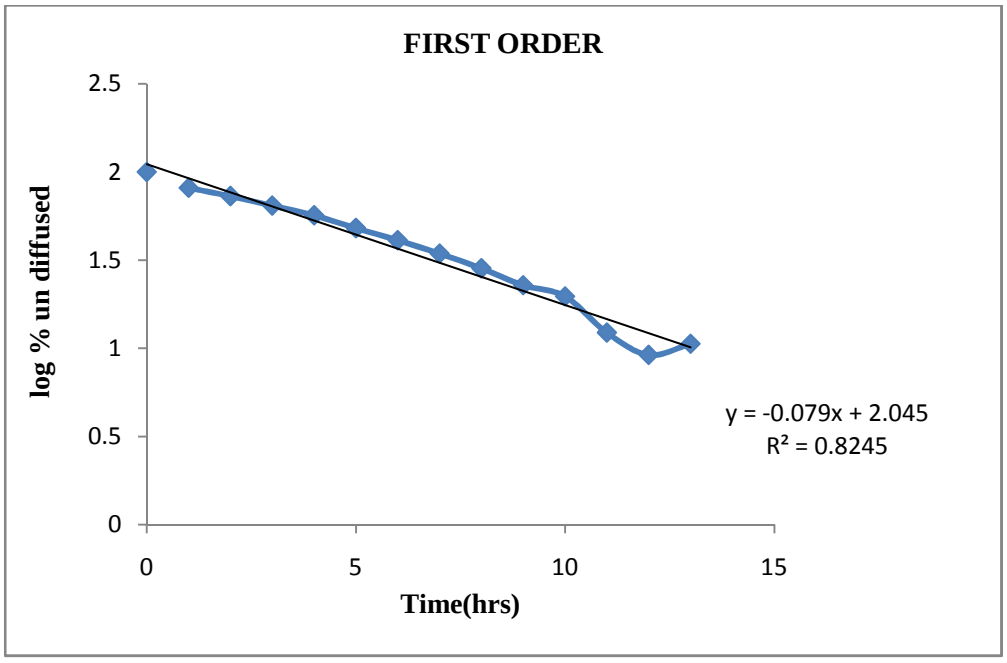


Figure 25: Higuchi Plot (F2)

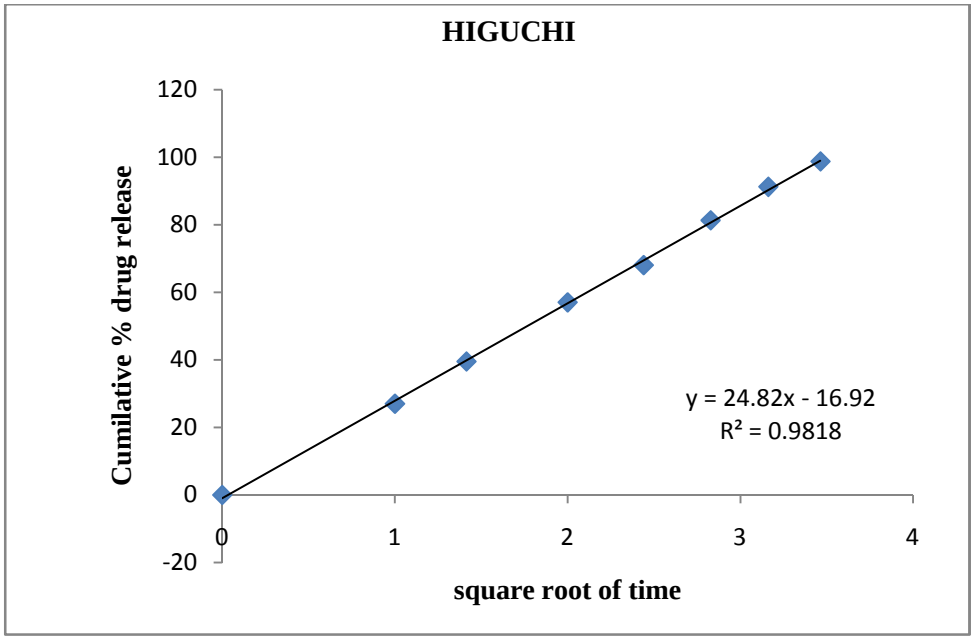
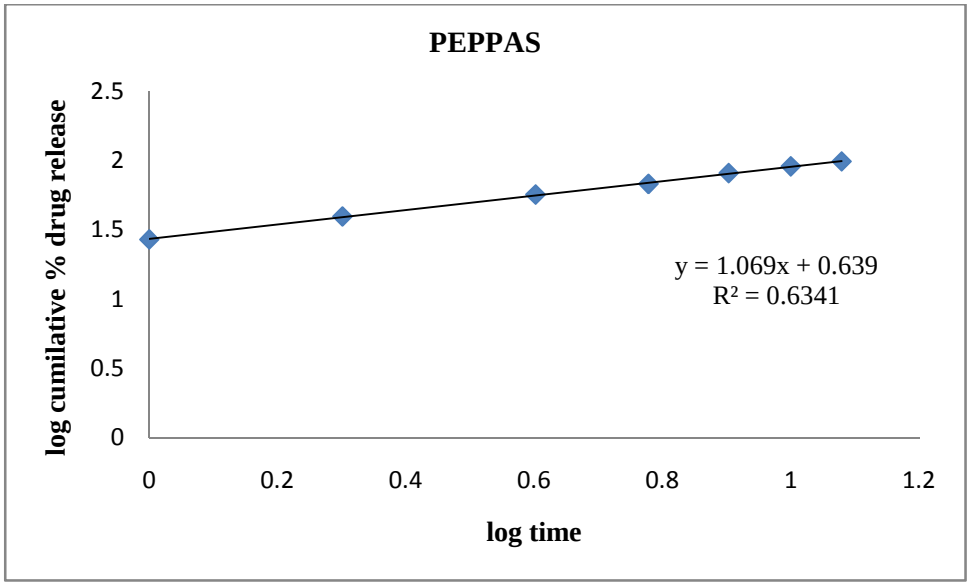


Figure 26: Korsemeyer Peppas Model (F2)



Kinetics of drug release

Table 27: Drug release kinrtics

Formulation	Zero-order	First-order	Higuchi	Krosmeyer peppas	
				R^2	N
F2	0.9877	0.8245	0.9818	0.6341	0.5062

The results of R^2 for zero order and first order were obtained as 0.9877 and 0.8245. Based on that we confirmed that the optimised formulation followed zero order release.

The drug release was diffusion controlled as the plot of optimized formulation F2 was found 0.9818 as regression coefficient in Higuchi plot.

From Korsemeyer- peppas's plot the release exponent value N was found as 0.506 and it was confirmed as the release of drug from formulation was founded as anomalous non-fickian transport of diffusion.

7.9 ACCELERATED STABILITY STUDIES

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection.

During the stability studies the product was exposed to normal conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product was stored under extreme conditions of temperature. In the present study, stability studies were carried out on formulation F2.The tablets were stored at 40 ± 2^0 C 75 ± 5 % RH for a duration of three months.

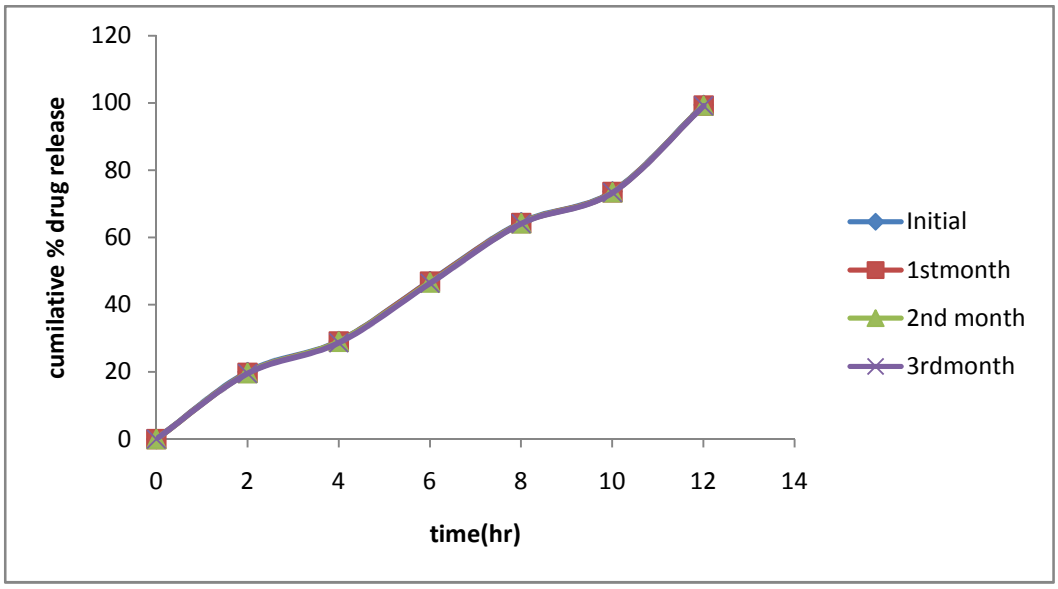
The selected formulation was evaluated for stability studies. The formulation were stored at 40°C at 75%RH for 3 months and analysed for their physical parameters, drug content and friability after 3rd month the data were showed in table no 29.

Table no 29: Physical parameters studies

	Drug content (%)	Hardness (kg/cm^2)	Friability (%)
After 1 month	99.33±0.17	4.1±0.3	0.45
After 2 months	99.12±0.15	4.0±0.42	0.46
After 3 months	99.12±0.15	4.0±0.42	0.46

Table No 30: In Vitro Dissolution Studies

Time(hr)	Initial	1st month	2nd month	3rd month
0	0	0	0	0
2	19.97	19.71	19.64	19.52
4	29.13	29.01	28.97	28.65
6	47.00	46.87	46.53	46.37
8	64.46	64.26	64.15	64.07
10	73.61	73.44	73.35	73.30
12	99.33	99.20	99.15	99.12



From the above tables (table no 29 & 30) it was observed there is no much change in its physical properties and %drug release. Hence formulation(F2) conformed stable.

SUMMARY AND CONCLUSION

- The preformulation parameters like organoleptic properties, angle of repose, bulk density, tapped density, Hausner's ratio, carr's index and compressibility index of pure drug was evaluvated and complied with the pharmacopoeial specifications.
- FTIR studies showed there was no interaction between drug and polymer.
- Gastro retentive floating matrix tablets of Losartan potassium were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC K15M.,HPMC 100M.
- The formulated batches were evaluated for physicochemical parameters, floating properties and dissolution profiles. From the evaluation results, it was observed that the tablets contain the higher viscosity HPMC showed long floating lag time when compared to tablets prepared with lower viscosity HPMC. The physical properties like hardness, weight variation and friability of majority of the batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 95 – 100%.
- *In vitro* dissolution study of all the formulations was done in 0.1 N HCL. The release rate was faster with lower viscosity grades of HPMC, probably owing to less polymer entanglement and less gel strength and also to the larger effective molecular diffusion area at lower viscosity as compared with higher viscosity grades of HPMC.
- The tablets containing HPMC K4M (F2) showed satisfactory results with short floating lag time (68 sec) total buoyancy time more than 12 h, cumulative % drug release (99.33) and controlled drug release up to 12 h. So F2 was taken for kinetic studies.
- The kinetic studies were carried for formulation F2 showed high regression value of 0.9877 for zero order, 0.981 for Higuchi order (conforms non- Fickian sustained release) and N value greater than 5 (conforms

diffusion controlled) with complete release in 12 hrs made it to select as an optimized formulation compared with other formulations.

- The accelerated stability was carried for F2 formulation and shown no much change in physical parameters and cumulative % drug release. Hence formulation F2 conformed as stable.
- Hence it was concluded that formulation F2 choosen as optimum formulation.
- However *In vivo* studies and development of suitable packaging material are made for future continuation of this experimental work.

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